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DIABETES MELLITUS

A CONTRIBUTION TO ITS EPIDEMIOLOGY BASED CHIEFLY ON MORTALITY STATISTICS *

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AND
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NEW YORK

INTRODUCTION

Although the term, epidemiology, has in the past been applied generally, if not exclusively, to the study of communicable diseases, so far as concerns their development among groups, or their manner of transmission from the infected or the carrier to the susceptible person, the methods of such investigations can often be employed with advantage in analyzing the causes and distribution of other diseases. The essential and distinctive feature of epidemiology is the study or knowledge of that part of the natural history of a disease which determines its occurrence or distribution quantitatively and qualitatively in groups of persons, particularly as one case of sickness is related to others, by some common factor of age, sex, race, color, occupation, geographical distribution, or determining element in heredity, environment or hygiene, distinct from the study of disease as it affects the life history of the person by modifying the structures and functions of the human body.

A limitation of accuracy in any statements based on mortality statistics must be accepted where the cause of death as given on the death certificate is without support from postmortem examination, or lacks corroboration through positive evidence of etiology as can often be obtained by direct inspection of lesions, with or without operation, or by clinical, microscopic or biologic examination of body tissues, fluids, etc., before death.

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* From the Department of Public Health Administration of Columbia University.

* Read before the Association of American Physicians, Atlantic City, May 7, 1924, and before the Section on Preventive and Industrial Medicine and Public Health at the Seventy-Fifth Annual Session of the American Medical Association, Chicago, June, 1924.

Tuberculosis is usually found to be the chief complicating fatal disease which may obscure the picture of diabetes deaths, but since tuberculosis has been, in general, steadily decreasing as a cause of death during the last fifty years, and diabetes has been increasing over the same period, we can presume that the accuracy in diabetes death rates has been increasing, so far as this factor is concerned.

Where diabetes is given as a primary cause of death, the following diseases have been the chief contributing causes in the order of frequency, as shown in Table 1, for the United States Registration Area of 1917 and for the City of New York in the years 1914 and 1920.

It is of some importance in this connection to recall the fact that it has been a standard practice by the Census Bureau, and by registrars of vital statistics generally throughout this country, to deal with certificates presenting more than one cause of death according to the

TABLE 1.—*Contributory Causes of Death in Diabetes*

	U. S. Registration Area, 1917 *	City of New York	
		1914 †	1920 ‡
Total deaths from diabetes	12,734	979	1,075
All contributing causes	6,080	316	457
Principal contributing causes	(4,480)	(297)	(282)
Gangrene	1,235	.....	.....
Bright's disease	951	126	75
Organic heart disease	812	67	84
Cerebral hemorrhage	397	.....	.....
Lobar pneumonia	273	15	10
Diseases of the arteries	223	26	40
Furuncle	200	.....	.....
Bronchopneumonia	170	23	19
Pulmonary congestion	116	.....	.....
Acute nephritis	103	9	7
Apoplexy (embolism and thrombosis)	.....	19	25
Surgical operations	.....	7	14
Diarrhea	.....	5	8

* U. S. Census Bureau Mortality Statistics, 1917.
† Annual Report of the Dept. of Health of the City of New York, 1914, p. 103.
‡ Annual Report of the Dept. of Health of the City of New York, 1920, p. 282.

Index of Joint Causes of Death, U. S. Bureau of the Census, 1914. According to this practice, diabetes takes precedence over all other causes with which it is reported jointly as a contributing cause, except diphtheria, pulmonary tuberculosis and typhoid fever. The error, if error there be in the inclusion of diabetes among the deaths reported from all forms of tuberculosis as a contributing cause, must indeed be small, since of 110,144 deaths from tuberculosis in the Registration Area as reported in the 1918 Census Mortality Report, pages 49 et seq., diabetes appears as a recorded complication in only 365 instances.

There is no wholly reliable way of proving that deaths from diabetes are more or less accurately recognized now than they have been at any time during the last sixty years. It may, however, be accepted as probable that diabetes has shared with other causes of death in the greater accuracy of clinical diagnosis, which is chiefly responsible in

the United States for a diminution in deaths reported under those categories or titles of the International List which are unsatisfactory, because of their indefiniteness and the inclusion of many unrelated and ill-defined groups, while there has been a corresponding increase in the proportion of all deaths accurately recorded under their proper and reasonably precise titles.

The frequency with which glycosuria is discovered by routine and special examinations of urine in the course of private and institutional medical practice has doubtless increased greatly in the last twenty years, and this, together with the increased frequency of blood sugar determinations, has probably caused a higher proportion of persons to be brought under medical supervision for disturbance of the function of sugar tolerance in recent years than was the case a generation ago.

We should expect that the advances in early detection of mild cases of glycosuria, of high blood sugar content, and of subjectively symptomless diabetes, together with the widespread interest in dietetic adjustment and medical regulation of food habits of such persons, would have the effect of diminishing the ratio of deaths attributable to diabetes rather than of increasing them in the population.

The duration of the disease, its characteristic symptomatology and the frequency with which its advanced stages bring the patient under medical care, all combine to reduce to a minimum those diagnostic errors which would lead to failure of its recognition as the cause of death.

The only substantial fact that may be accepted as lending force to an argument that deaths from diabetes have in the main been recorded with as much or greater accuracy than has been the case in other important causes of death, is the experience of Cabot[1] with the necropsies at the Massachusetts General Hospital, who observed that among the 3,000 necropsy cases studied, there was little evidence of omission of cause, or commission of error in those stated to be due to diabetes mellitus. (Other causes of death in which as high a percentage of accuracy occurred, i. e., 95 per cent., were leukemia, pernicious anemia, diphtheria, puerperal eclampsia, malaria, dementia paralytica and amebic dysentery.)

While the use of insulin may be postponing markedly the deaths of diabetic patients, it has not yet been shown that any permanent improvement in the death rate from this disease can be attributed solely to its use, and even if this favorable result should develop, the influence on death rates among the general population of cities or states in this country can hardly be expected to appear until at least the year 1924.

1. Cabot, Richard C.: Diagnostic Pitfalls Identified During a Study of Three thousand Necropsies, J. A. M. A. **59**:2295 (Dec. 28) 1912.

Evidence has been offered by the Metropolitan Life Insurance Company [2] to the effect that a reduction in the death rate from diabetes among their industrial policy holders, during the last half of 1923 and the first quarter of 1924, is possibly due to the widespread use of insulin in the last year. In any event, the discovery of insulin can hardly be considered to have introduced any error into the mortality data offered in this paper.

If any particular community differs in the percentages of its population living at the various age groups from the distribution of the population by these age groups in the country as a whole, or in other cities with which death rates are compared, an adjustment of death rates for age is necessary for accuracy. In the case of New York City, whatever change there has been in the years since 1866 in the age grouping can hardly have caused any error of overestimation in the diabetes death rates, for, as a matter of fact, the City of New York in 1920 had a larger percentage of its population under 40 years of age than any city in the United States with a population of 100,000 or over. There is a considerable error in the unadjusted general death rate of the city in the direction of an understatement. Because of the relative youth of its population, the error is likewise one of underestimation to an even greater degree in the specific death rate of diabetes, from the fact, as will be seen from the study of diabetes death rates for various ages, that the rates are much higher in the later decades of life, age groups which are represented in New York City by less than the standard percentage of the population in other cities or in the Registration Area.

If there is any error in drawing conclusions from the changes in the death rates of diabetes in the last sixty years, it is likely to be due to an understatement rather than an exaggeration in the reported deaths from this cause. It is probable that this error was greater in 1866, the first year for which rates are quoted for the city of New York, than in 1923.

It cannot be assumed that increase of deaths necessarily indicates an increase in the incidence of a disease, nor that an increase in the number of cases of a disease diagnosed will necessarily be expressed in an increase of the death rate of a disease, but rather the contrary, owing to the greater probability of successful arresting or curative treatment, as in the case of tuberculosis following earlier and more accurate diagnosis. In other words, the case mortality percentage of a disease which is amenable to curative resources is likely to fall as diagnosis becomes commoner in its early stages. This we may assume to have

2. Statistical Bulletin, New York Metropolitan Life Insurance Co., February, 1924.

been the case with diabetes, in which such remarkable advances have been made in diagnosis and treatment, during the last twenty years in particular.

The assumption, however, is valid that an increase in the death rate of a disease may be considered as indicating an actual increase in its incidence, during a period of time when clinical diagnosis and treatment have developed progressively in the direction of greater success in recognizing and arresting it in its mild or early stages, and in postponing death in patients whose condition has progressed beyond the possibility of cure.

Among the factors which have been commonly considered by students of diabetes to play any important rôle in its etiology, two, namely, obesity, or disproportionate weight for the age, sex, race and height of the person, and "nervous strain," presumed to exist when life is complicated, full of responsibility and difficult because of keen economic or industrial competition, are not revealed by the death certificate except to the extent that occupation or place of residence reported may imply a life of particular nervous hazard on the part of the deceased. Many questions of etiology receive but little illumination from mortality data unless supported by carefully prepared case histories. Similarly, the hereditary, familial or conjugal factors, if of any force in the causation of diabetes, cannot be satisfactorily studied by the use of general mortality statistics alone, and even when reliable data in a selected experience are offered in support of the theory that inheritance, family or conjugal relationships were of significance in causing diabetes such claims are commonly worthless by reason of the lack of evidence as to the dietary, occupational and other factors in the cases, which are often of more significance than the accidental relationships of birth or marriage.

Mortality data will be presented which it is believed will make clear that a consistent and great actual increase in the diabetes death rate has occurred in New York City between 1866 and 1923, and similarly in many other population groups in recent years. Some of the causative factors will be presented and discussed.

THE INCREASE IN DEATH RATES FROM DIABETES IN RECENT YEARS

A sufficient reason for studying the deaths from diabetes in New York City at this time is the considerable shift in relative importance, numerically, of the leading causes of death which has dropped tuberculosis from first to fourth place and has brought diabetes up to tenth place (Table 2).

Expressed otherwise, we find that while one death from diabetes was recorded in 1866 for each 2,437 deaths from all causes, in the year 1923, one death from diabetes was recorded for each fifty-one deaths from all causes.

In many of the cities of this country, where notable reduction in deaths from tuberculosis has occurred, we find there is now one death from diabetes for every four or five deaths from tuberculosis.

In the registration area of the United States in the last forty years there has been a change from 2.8 to 16.1 in the death rate from diabetes per 100,000, of population, while the death rate from all causes has

TABLE 2.—*Chief Causes of Death, City of New York, 1923*

Organic heart diseases	14,321
Pneumonia and bronchopneumonia	8,231
Cancer	6,287
Tuberculosis, all forms	5,673
Violent deaths (excluding suicide, including homicide)	4,502
Bright's disease and nephritis	4,367
Congenital debility and malformations	3,723
Diseases of arteries	3,250
Diarrhea under 5 years	1,534
Diabetes	1,360

fallen steadily during this period. There has been a still greater change in the percentage of all deaths represented by those from diabetes; in 1921 the deaths from diabetes represented 1.4 per cent. of all deaths in the Registration Area, while in 1880 deaths from diabetes amounted to but 0.14 per cent. of all deaths in the Registration Area of that date, a change amounting to 900 per cent. of the ratio of 1880.

Of the principal causes of death in the Registration Area of the United States, 1920, diabetes appears in the twelfth place, as will be seen from the specific death rates per 100,000 given in Table 3.

TABLE 3.—*Death Rates per Hundred Thousand of Population from the Chief Causes of Death in the Registration Area of the United States, 1920* *

Organic diseases of heart	141.9
Pneumonia and bronchopneumonia	137.3
Tuberculosis, all forms	114.2
Bright's disease and nephritis	89.4
External causes (violent deaths including suicide and homicide)	88.8
Cancer	83.4
Cerebral hemorrhage	80.9
Influenza	71.0
Congenital debility and malformations	69.9
Diseases of arteries	22.8
Puerperal state	19.2
Diabetes	16.1

* U. S. Census Bureau Mortality Rates, 1910-1920.

That the importance of the increasing mortality from diabetes has long been recognized by the Census Bureau can be seen from the following quotations from the volumes on Mortality Statistics of 1906, 1907 and 1909.

1906. "Among the old Registration States there appears to be a decided tendency to an increase in mortality from this cause. These

were, in order of highest death rate, Connecticut (18.8), Maine (16.8), Massachusetts (16.1), New York (16.0), Michigan (13.7), New Jersey (12.8), Indiana (11.0).

"While the mortality from this disease is not great, its general increase throughout the country is significant and may be compared with the similar increase shown for cancer, a disease whose age incidence resembles that of diabetes."

1907. "This rate (13.9 per 100,000 for diabetes, 1907) is low as compared with the rates for tuberculosis, cancer, and other important diseases, but the mortality from diabetes is of increasing significance, as being due to a fairly well marked and distinctive type of disease and one likely to show further increase, dependent on the greater number of persons at older ages in the population. The disease is one of later middle life, is intimately dependent on the conditions affecting the nervous system, as well as the nutrition of the person, and may be one of those diseases which the sanitarians of the future will successfully restrict by directing their efforts against unhygienic conditions of living, both mental and physical."

1909. "The relative increase in the death rate from diabetes (45.5 per cent.) was considerably greater than that in the death rate from cancer, but the total number of deaths from this cause was much smaller, and therefore the increase is of less importance numerically."

United States Bureau of the Census: Mortality Rates, 1910-1920, 1923, pp. 87 and 88: "For the Registration States of 1900 the death rates from diabetes show a steady trend upward, the adjusted rate for 1900 being 10.4 per 100,000 population, the rate for 1910 being 16.16, and the rate for 1920 reaching 18.7.

"For both the white and colored in the Registration Area and Registration Cities, and the rural part of the Area, the death rates from diabetes increased generally in the decade: (for the white, from 15.3 to 16.8 in the Registraion Area; from 16.4 to 19.6 in the Registration Cities; and from 13.7 to 14.1 in the rural districts, and for the colored in the respective areas from 7 to 7.9; from 8.3 to 12.7, and from 3.2 to 5.2)."

DEATHS FROM DIABETES IN THE CITY OF NEW YORK FROM 1866 TO 1923

In the years from 1866 to 1923, inclusive, there were recorded by the registrar's office of the Department of Health of the City of New York, 23,254 deaths due to diabetes.

Chart 1 and Table 4 give the story at a glance, and present at the same time a picture of the fall in the general death rate, i. e., the deaths from all causes for each 1,000 of the population, from 36.86 to 11.72 (a difference of 68.2 per cent.); the rise in the specific death rate from

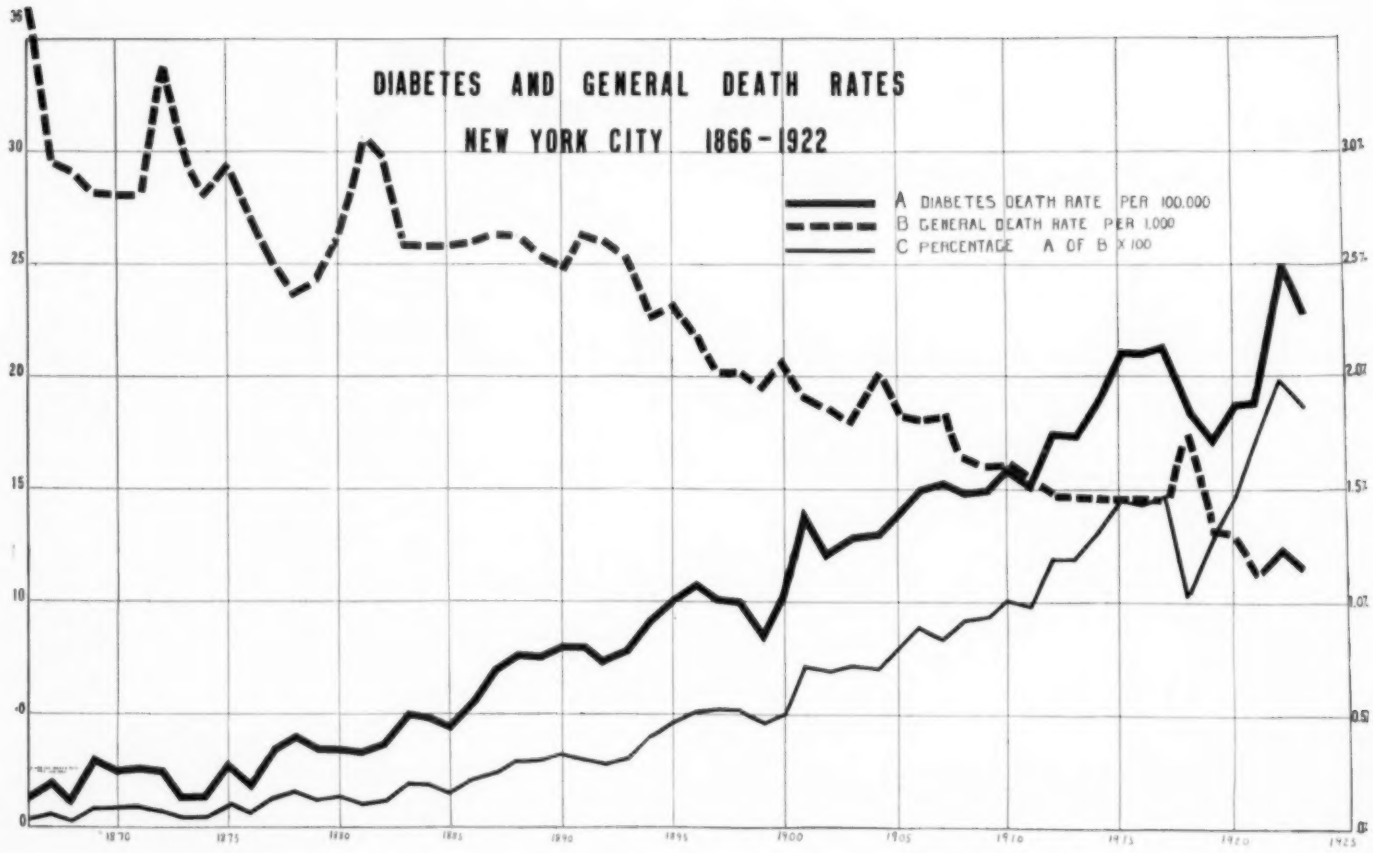

Chart 1.—Death rates from diabetes, and from all causes, New York City, 1866-1923.

diabetes for each 100,000 of the population from 1.5 to 22.9 (a difference of 1,426.7 per cent.), and the change in relation of deaths from diabetes to deaths from all causes, from 0.041 to 1.96 per cent. (a difference of 4,631.9 per cent.).

TABLE 4.—*Deaths and Death Rates, All Causes, and from Diabetes, New York City from 1866 to 1923*

Year	Population	Total Deaths, All Causes	Crude Death Rate per 1,000	Diabetes Deaths			Diabetes Death Rate per 100,000	Percentage, Diabetes Deaths of All Deaths	Age Groups					
									0 to 19		20 to 44		45+	
				Total	Male	Female			M.	F.	M.	F.	M.	F.
1866	769,567	26,567	36.86	11	7	4	1.5	0.041	3	1	1	1	3	2
1867	812,748	23,159	31.89	14	9	5	1.9	0.061	1	1	1	4	7	0
1868	855,929	24,889	29.24	18	4	4	1.1	0.032	0	2	2	2	2	0
1869	899,100	25,167	28.08	22	13	9	3.0	0.088	2	0	6	3	5	6
1870	942,292	27,175	28.80	24	14	10	2.5	0.089	0	0	7	2	7	8
1871	962,210	26,976	28.22	25	16	9	2.6	0.093	3	2	9	2	4	5
1872	982,128	32,647	33.70	25	16	9	2.5	0.077	1	0	4	4	11	5
1873	1,002,046	29,084	29.63	13	7	6	1.3	0.045	0	0	4	1	3	5
1874	1,021,964	28,727	27.89	14	7	7	1.4	0.049	0	0	5	3	2	4
1875	1,041,886	30,709	29.40	31	21	10	2.9	0.101	1	2	9	3	11	5
1876	1,074,824	29,152	27.11	19	8	11	1.7	0.065	1	0	2	6	5	5
1877	1,117,762	26,203	23.66	35	24	11	3.3	0.134	6	1	4	4	14	6
1878	1,150,700	27,008	23.67	42	25	17	4.0	0.156	1	1	9	3	15	13
1879	1,183,638	28,342	24.13	37	21	16	3.4	0.131	2	0	4	7	15	9
1880	1,206,577	31,937	26.42	44	24	20	3.5	0.138	1	3	6	4	17	13
1881	1,246,011	38,624	30.75	43	29	14	3.4	0.111	0	0	12	1	17	13
1882	1,283,870	37,924	29.61	46	29	17	3.7	0.121	3	0	7	7	19	10
1883	1,322,880	24,011	25.81	68	34	34	5.1	0.200	2	2	12	13	20	19
1884	1,363,075	35,034	25.83	68	41	27	4.9	0.194	1	2	10	5	30	20
1885	1,404,401	35,682	25.56	63	35	28	4.5	0.177	1	1	11	6	23	21
1886	1,447,166	37,351	26.00	82	47	35	5.6	0.220	5	4	13	7	29	24
1887	1,491,137	38,933	26.33	105	52	53	7.0	0.270	1	1	7	8	44	44
1888	1,536,444	40,175	26.39	117	61	56	7.6	0.292	5*	4*	10†	8†	46	44
1889	1,566,801	39,679	25.36	118	71	47	7.5	0.297	5*	1*	13†	8†	53	38
1890	1,612,559	40,103	24.87	130	72	58	8.0	0.324	5	3	17	10	50	45
1891	1,659,654	43,659	26.31	130	64	66	8.0	0.298	2	5	10	11	52	50
1892	1,708,124	44,329	25.95	123	66	57	7.2	0.278	6	3	15	14	45	40
1893	1,758,010	44,486	25.30	137	76	61	7.7	0.308	4	3	12	13	60	45
1894	1,809,353	41,175	22.76	166	87	79	9.2	0.403	0	4	22	11	65	64
1895	1,879,195	43,420	23.18	203	95	108	10.0	0.468	3	6	21	17	71	85
1896	1,934,077	41,622	21.84	214	98	116	11.0	0.514	5	1	19	8	74	107
1897	1,990,562	38,877	20.03	202	95	107	10.1	0.520	3	5	21	13	71	89
1898‡	3,438,899	66,294	20.26	345	153	192	10.0	0.521	8	7	37	26	108	159
1899	3,356,722	65,343	19.47	301	148	153	8.4	0.461	10	7	40	17	98	129
1899	3,356,722	65,343	19.47	301	148	152	8.4	0.461	10	7	40	17	98	129
1900	3,446,042	70,872	20.57	357	169	188	10.0	0.503	6	8	38	32	125	148
1901	3,544,079	70,720	19.90	503	269	234	14.0	0.712	9	2	69	37	191	195
1902	3,665,825	68,112	18.58	471	212	259	12.0	0.692	13	10	48	34	151	215
1903	3,781,423	67,864	17.95	488	232	256	12.8	0.721	2	8	57	42	173	206
1904	3,901,023	78,060	20.01	549	233	316	13.0	0.703	11	14	40	50	182	252
1905	4,025,742	73,714	18.31	589	266	323	14.0	0.799	7	11	57	47	202	265
1906	4,166,556	76,203	18.29	632	281	371	15.0	0.856	12	11	49	53	220	307
1907	4,314,237	79,305	18.36	664	251	413	15.3	0.838	13	15	35	53	203	345
1908	4,469,248	73,072	16.35	670	290	380	14.9	0.916	16	7	46	48	228	325
1909	4,632,078	74,105	16.00	696	288	408	15.0	0.939	14	15	48	52	226	341
1910	4,788,009	76,742	16.04	768	320	448	16.0	1.002	8	18	52	65	260	365
1911	4,873,211	75,423	15.48	739	316	423	15.1	0.981	14	10	59	60	243	353
1912	5,961,205	73,008	14.71	870	362	508	17.5	1.192	11	19	59	59	292	430
1913	5,049,199	73,902	14.64	884	366	518	17.5	1.196	16	18	63	52	287	448
1914	5,137,193	74,803	14.56	979	409	570	19.0	1.309	19	20	56	70	334	480
1915	5,225,189	76,193	14.58	1,109	462	647	21.2	1.455	18	21	81	69	363	557
1916	5,313,181	77,801	14.64	1,119	470	649	21.0	1.437	15	14	75	81	380	554
1917	5,401,175	78,575	14.55	1,153	473	680	21.3	1.467	15	14	74	77	384	516
1918	5,489,169	98,119	17.88	1,011	410	601	18.4	1.030	28	18	79	88	303	495
1919	5,577,163	74,433	13.35	955	380	575	17.1	1.284	18	17	71	69	291	489
1920	5,665,157	73,249	12.93	1,075	411	664	18.9	1.468	29	22	58	86	324	556
1921	5,751,859	64,257	11.17	1,120	428	692	19.0	1.74	25	25	82	74	321	593
1922	5,830,738	69,690	11.93	1,448	581	867	25.0	2.08	30	24	82	99	469	744
1923	5,927,617	69,452	11.72	1,360	512	848	22.9	1.96	..	..	..	..	..	..

* Age group for 1888 and 1889, from 0 to 24 years.
† Age group for 1888 and 1889, from 25 to 44 years.
‡ Greater City for all five boroughs 1898 and following

It will be recalled that the main factors which have brought about the reduction in the general death rate in New York have been the control of the bacterial diseases of the intestinal tract, the diminution in incidence and death rates from the acute communicable diseases of childhood, reduction in tuberculosis and infant mortality, and great improvement in the economic and sanitary standards of housing and food supplies.

In the course of the increase in death rates from diabetes over this long period, there are two periods of sudden and considerable reductions in the rates, followed by even more rapid rises to higher rates than before the fall. The first of these sudden falls and rises coincided with the period of the influenza epidemic from 1898 to 1901, and in all probability represents the effect of this highly fatal infection on persons of the ages chiefly afflicted by diabetes, i. e., those over 40 years of age who suffered particularly in that epidemic. Many persons who would have died of diabetes were carried off by influenza during the years in question.

The halt in the increasing diabetes death rate, which occurred in the years 1916 and 1917, was followed by a sharp drop in 1918, 1919 and 1920, the year 1922 showing the highest rate yet recorded. From experience in other countries, which suffered between 1914 and 1917 from interference and limitation in their food supplies, it seems probable that the halt in the rising diabetes death rate in 1916 and 1917 was related to the voluntary and enforced restrictions in food used, while the great drop which followed for three years was due to the influenza epidemic and the effect it had on all death rates of persons over 45 years of age, even though the heaviest mortality from influenza in this pandemic was in earlier decades of life.

In the face of the records, it is difficult to accept as a probable explanation of increasing diabetes death rates an increase of infectious or febrile diseases.

ANALYSIS BY AGE AND SEX

Developing this general statement of deaths to give those facts which are essential to any complete picture of a disease, we offer an analysis of deaths by age and sex.

In Charts 2, 3 and 4 and Tables 5 to 16 the facts are set forth.

Charts 2 and 3 record graphically by the semilogarithmic and arithmetic methods, respectively, the specific diabetes death rates for three age groups in the years 1866, 1875, 1880, 1895, 1900, 1910 and 1920, for which an enumeration of the city's population provided the number of persons living at each age group. The facts of population and deaths at the different ages for these seven years will be found in Table 5.

TABLE 5.—*Deaths and Death Rates per Hundred Thousand Population from Diabetes in Selected Age Groups at Census Years, New York City*

Year	Population			Deaths from Diabetes			Diabetes Death Rates		
	0 to 19 Years	20 to 44 Years	45 Years and Over	0 to 19 Years	20 to 44 Years	45 Years and Over	0 to 19 Years	20 to 44 Years	45 Years and Over
1866	319,654	306,339	100,846	4	2	5	1.25	0.65	4.9
1875	442,584	446,812	152,490	3	12	16	0.68	2.68	10.5
1880	495,260	519,391	190,693	4	10	30	0.81	1.93	15.7
1895	660,313	874,355	284,331	9	38	156	1.31	4.36	55.0
1900	1,356,049	1,530,239	545,478	14	70	273	1.03	4.57	50.3
1910	1,825,390	2,145,583	789,108	26	117	625	1.42	5.45	79.2
1920	2,045,984	2,488,415	1,077,844	51	144	880	2.49	5.78	81.7

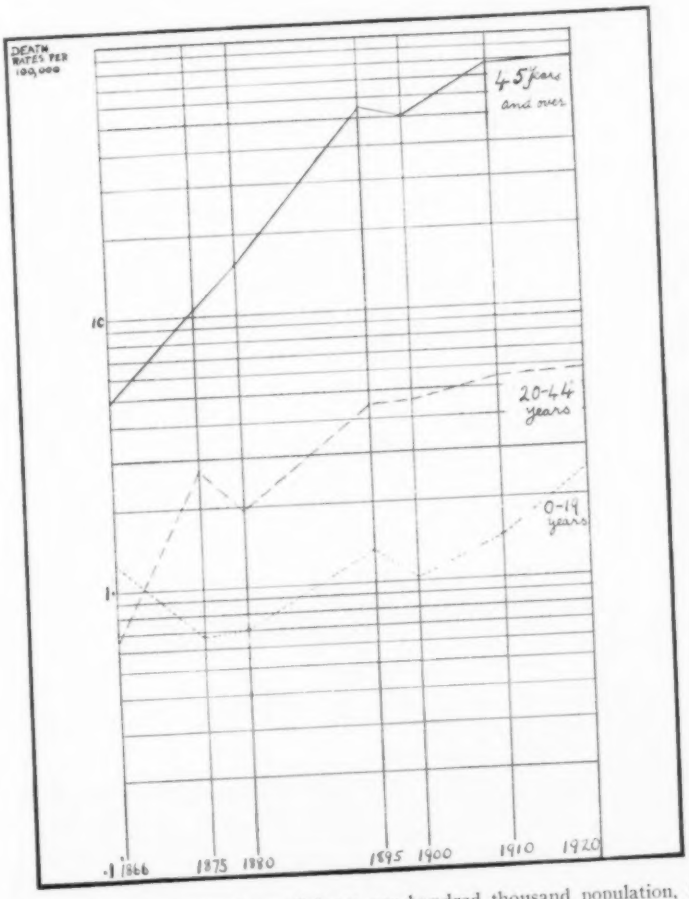

Chart 2.—Death rates from diabetes per hundred thousand population, New York City, by certain age groups at census years (semilogarithmic method).

It will be seen that for each of the three age groups (from birth to 19 years, from 20 to 44 years, and 45 years and over) the net result is a marked rise in death rates, greatest among the latter decades of life and least among those of 19 years of age and under. The ratio

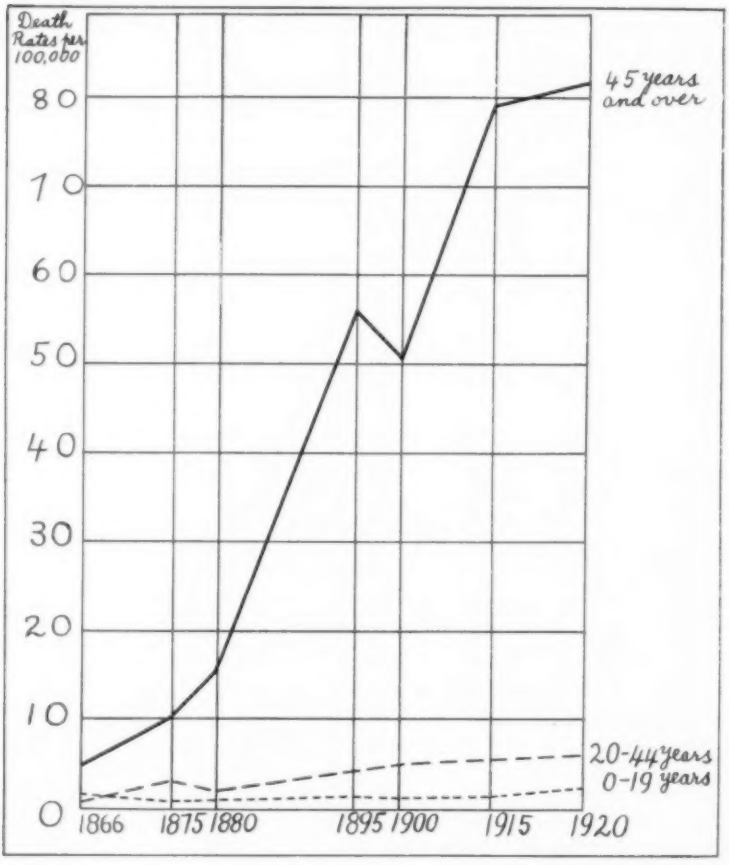

Chart 3.—Death rate from diabetes per hundred thousand population, New York City.

of change is expressed graphically with greater accuracy by the logarithmic Chart 2.

Table 6 presents for these same seven individual census years the evidence of change in the percentages of the population and of diabetes deaths represented in the three chosen age groups, from which it will be seen that in the forty-five years (from 1875 to 1920) the percentage

TABLE 6.—*Diabetes Deaths Distributed in Selected Age Groups, New York City*

Year	Percentage of All Population Represented in Each Age Group in Census Years			Percentage of All Diabetes Deaths Falling in the Same Age Groups and Years		
	0 to 19 Years	20 to 44 Years	45 Years and Over	0 to 19 Years	20 to 44 Years	45 Years and Over
1875	42.0	42.8	14.6	9.6	38.7	51.7
1880	41.0	43.0	16.0	9.1	22.7	68.2
1895	37.4	47.0	15.0	4.4	18.7	76.9
1900	39.0	45.0	16.0	3.9	19.6	76.5
1910	38.0	45.0	17.0	3.3	15.2	81.5
1920	36.0	44.0	19.0	4.7	13.4	82.0

of the population represented by the youngest age group (19 years and under) fell from 42.0 per cent. in 1875 to 36.0 per cent. in 1920, and that during the same time the percentage of all diabetes deaths occurring in this young group fell from 9.6 to 4.7 per cent. On the other hand,

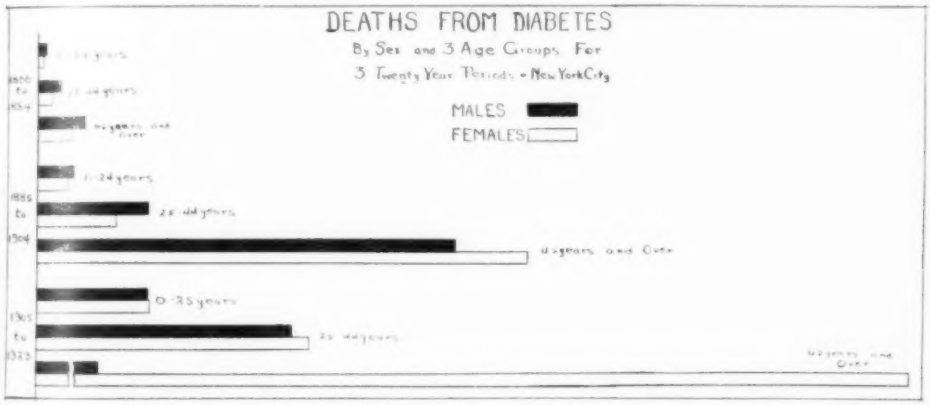

Chart 4.—Deaths from diabetes by sex and three age groups for three twenty year periods, New York City.

TABLE 7.—*Deaths from Diabetes by Sex and Three Age Groups for Three Consecutive Periods of Years, New York City*

Year	0 to 24 Years		25 to 44 Years		45 Years and Over	
	Male	Female	Male	Female	Male	Female
1866 to 1884	39	25	103	68	206	145
1885 to 1904	160	130	464	339	1,711	2,000
1905 to 1923	468	473	1,045	1,118	5,763	8,904

the age group of 45 years and over represented 14.6 per cent. of the entire population in 1875 and 19 per cent. in 1920, during which time the percentage of diabetes deaths occurring at these ages rose from 51.7 to 82 per cent.

Again from a study of Chart 4 and supporting table (Table 7), it will appear that while the deaths of males from diabetes exceeded those

of females at each of the chosen age groups in the 19 years, from 1866 to 1884, in the period from 1905 to 1923, the deaths of females from this cause outnumbered the males at each age group, and to a greater degree at advancing ages, and out of proportion to changes in the sex distribution of the population. In 1920 the difference in percentages of male and female populations of New York City was only 0.2 per cent.

TABLE 8.—*Percentage of Diabetes Deaths Occurring in Specific Age Groups in New York City, by Periods of Years and Individual Years by Sex, to Show What Percentage of the Diabetes Deaths Occur at Certain Ages, and in Each Sex*

Year	Sex	0 to 19 Years, per Cent.	20 to 44 Years, per Cent.	45 to 64 Years, per Cent.	65 Years and Over, per Cent.
1866 to 1887	Male	7.2	29.9	43.2	19.4
	Female	6.5	26.9	41.8	24.7
	Total	6.9	28.7	42.7	21.7
1890 to 1900	Male	4.62	22.4	46.0	26.9
	Female	4.4	14.5	48.4	32.7
	Total	4.5	18.3	47.1	29.9
1901 to 1917	Male	3.9	17.6	51.2	27.3
	Female	3.1	12.8	51.7	32.4
	Total	3.4	14.8	51.5	30.3
1918	Male	6.8	19.3	48.7	25.1
	Female	2.99	14.6	51.7	30.6
	Total	4.5	16.5	50.6	28.4
1919	Male	4.7	18.7	45.2	31.3
	Female	2.95	12.0	49.0	35.9
	Total	3.6	14.7	47.5	34.2
1920	Male	7.06	14.1	49.2	29.7
	Female	3.3	12.9	50.1	33.8
	Total	4.75	13.4	49.7	32.2
1921	Male	5.8	19.2	49.1	25.9
	Female	3.6	10.7	54.6	31.1
	Total	4.5	13.9	51.8	29.1
1922	Male	5.2	14.1	49.5	31.1
	Female	2.77	11.4	52.7	33.2
	Total	3.7	12.5	51.3	32.4

Table 8 confirms the story of the former tables to the effect that during the last 57 years in New York City, the proportion of all diabetes deaths under 20 years of age has remained about stationary, with the proportion of deaths among males higher in the first 20 years of life. At the ages of 45 years and over, the proportion of all diabetes deaths has increased, and those of females at a greater rate than those of males.

The great increase in specific diabetes death rates by age groups for females after 45 years of age is seen with even more detail in Table 9, although the period for comparison is only the ten years between 1910 and 1920.

It would appear that after the age of 45 among men, the situation in New York City so far as diabetes is concerned had improved, except for the age group 75 years and over.

TABLE 9.—*Diabetes Death Rates per Hundred Thousand by Sex and Age Groups, 1920 and 1910, New York City*

	Both Sexes		Males		Females	
	1920	1910	1920	1910	1920	1910
All ages: Adjusted	17.0	23.9	.....	.....	.....	.....
Crude	23.63	18.78	18.41	15.95	28.82	21.60
Under 5	1.6	0.6*	1.8	0.8*	1.4*	0.4*
5 to 9	3.2	0.9*	4.1	0.9*	2.2	0.9*
10 to 14	3.2	1.7	2.8	0.9*	3.6	2.4
15 to 19	3.3	2.4	4.1	0.9*	2.6	3.7
20 to 24	4.2	2.8	1.6*	2.4	6.4	3.2
25 to 34	4.87	4.4	4.6	3.8	5.1	5.1
35 to 44	10.2	9.8	8.8	8.4	11.7	11.4
45 to 54	46.1	45.3	37.9	39.4	54.8	51.6
55 to 64	131.7	128.4	96.3	107.5	167.1	148.4
65 to 75	236.7	192.7	178.7	188.0	287.3	196.8
75 and over	247.3	220.3	212.1	188.0	272.5	242.9

* Rates for deaths numbering less than five, U. S. Census Bureau Mortality Rates, 1910-1920, p. 526.

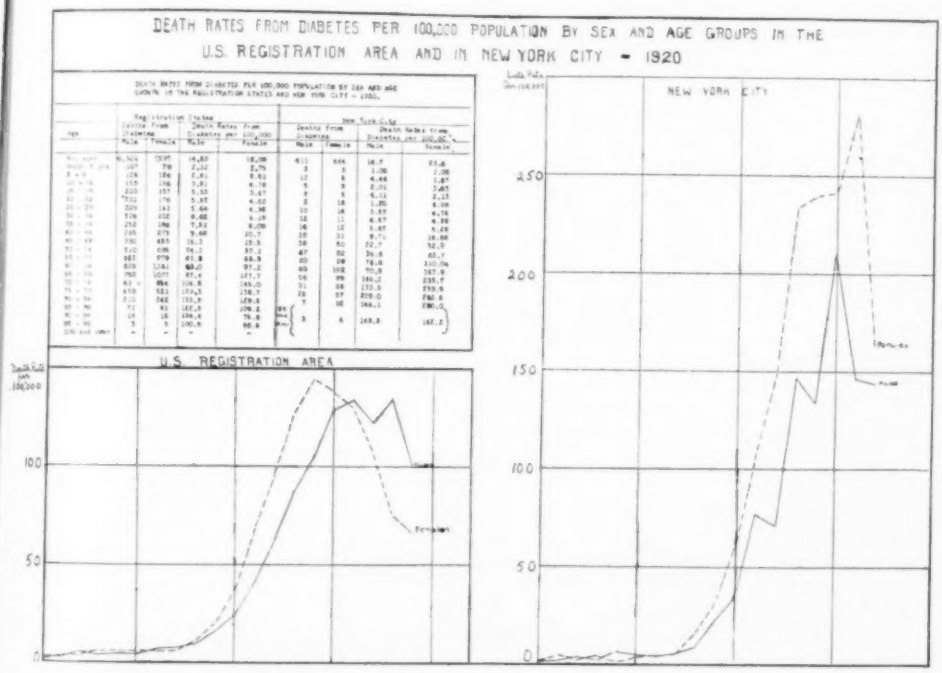
DEATH RATES FROM DIABETES PER 100,000 POPULATION BY SEX AND AGE GROUPS IN THE U.S. REGISTRATION AREA AND IN NEW YORK CITY - 1920
U.S. REGISTRATION AREA
NEW YORK CITY
250
200
150
100
50
0

Chart 5.—Deaths from diabetes by sex and five year age groups, New York City.

In Table 10 and Chart 5 where the experience of the Registration States and of New York City is compared by five year age groups for 1920, it is made clear that after the age of 40 women show higher diabetes death rates, except that males in the Registration Area over 80 years of age again take the lead.

TABLE 10.—*Death Rates From Diabetes per Hundred Thousand Population by Sex and Age Groups in the Registration States and New York City, 1920*

Age	Registration States: Deaths from Diabetes		Registration States: Death Rates from Diabetes per 100,000		New York City*: Deaths from Diabetes		New York City*: Death Rates from Diabetes per 100,000	
	Male	Female	Male	Female	Male	Female	Male	Female
All ages	6,301	7,597	14.83	18.09	411	664	14.7	23.6
Under 5	107	79	2.32	1.75	3	3	1.06	1.08
5 to 9	126	124	2.81	2.81	12	5	4.46	1.87
10 to 14	159	196	3.81	4.76	5	9	2.01	3.65
15 to 19	203	137	5.53	3.67	9	5	4.11	2.13
20 to 24	201	176	5.57	4.62	3	18	1.20	6.08
25 to 29	209	161	5.64	4.34	10	14	3.57	4.74
30 to 34	226	202	6.62	6.19	12	11	4.57	4.39
35 to 39	252	186	7.51	6.00	14	12	5.67	5.28
40 to 44	265	273	9.68	10.7	19	31	9.71	16.88
45 to 49	392	433	15.3	19.5	38	50	22.7	32.9
50 to 54	510	695	24.2	37.1	47	82	34.6	62.7
55 to 59	662	978	41.8	68.3	69	98	76.6	110.04
60 to 64	828	1,161	63.0	97.2	48	102	70.8	147.9
65 to 69	783	1,077	87.4	127.7	56	99	146.2	233.7
70 to 74	616	854	104.5	145.0	31	66	133.5	239.5
75 to 79	459	521	129.3	138.7	25	37	209.0	240.5
80 to 84	210	242	133.9	129.5	7	16	146.1	280.0
85 to 89	71	81	122.3	108.2	85 yr. and over	3	6	143.3	162.2
90 to 94	18	15	134.6	75.6					
95 to 99	3	3	100.8	66.5					
100 and over	..	..	..	..					

* The rates calculated on population groups as recorded in 1920, U. S. Census, and deaths from diabetes, as reported by New York City Department of Health.

Table 11, dealing with the population of the Registration States of 1900 for the years 1900, 1910 and 1920, as well as Chart 6 for the years from 1910 to 1920, add more convincing evidence of the predominant and increasing hazard of diabetes among women and particularly among those over 45 years of age.

TABLE 11.—*Death Rates from Diabetes per Hundred Thousand Population in the Registration States, 1910 **

Age	Both Sexes			Males			Females		
	1920	1910	1900	1920	1910	1900	1920	1910	1900
All ages: Adjusted	18.7	16.6	10.4	15.9	15.0	10.8	21.0	17.9	10.1
Crude	20.6	17.6	11.0	17.3	15.8	11.3	23.9	19.5	10.7
Under 5	2.5	2.4	2.1	2.8	2.8	2.3	2.2	2.0	1.8
5 to 9	3.3	3.5	2.4	3.6	3.3	2.2	3.1	3.7	2.5
10 to 14	4.9	4.4	4.2	4.2	4.2	4.1	5.7	4.5	4.4
15 to 19	5.3	5.3	4.5	5.8	4.9	5.6	4.7	5.7	3.5
20 to 24	5.1	4.2	4.0	5.7	4.8	3.8	4.6	3.5	4.1
25 to 34	5.6	5.6	5.0	5.9	5.8	5.3	5.4	5.3	4.8
35 to 44	9.2	9.0	6.8	9.2	9.2	7.8	9.2	8.8	5.8
45 to 54	30.0	27.2	16.4	23.8	25.5	15.5	36.6	29.0	17.3
55 to 64	80.9	75.9	40.4	63.1	63.9	37.6	99.1	88.1	43.1
65 to 74	141.5	117.8	67.2	111.0	103.2	71.1	170.6	131.8	63.5
75 and over	153.1	118.6	68.9	149.2	103.4	88.3	156.3	131.5	51.9

* U. S. Census Bureau Mortality Rates, 1910-1920, p. 87.

Table 12 shows how with advancing life expectancy, and possibly also in parts as a result of improved skill in medical care and earlier detection of the disease, the median age at death of diabetics has been advanced in the Registration States 2.1 years among men and 4.4 years among women in the last twenty years (from 1900 to 1920).

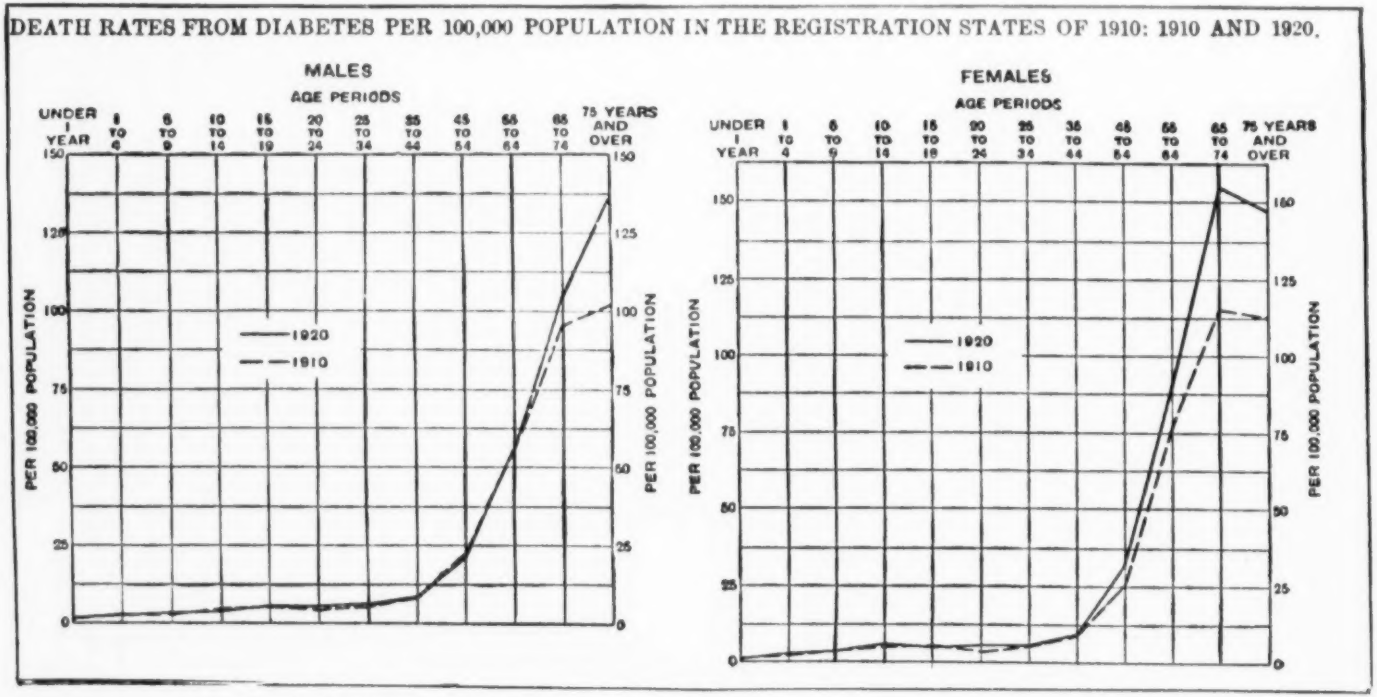

Chart 6.—Death rates from diabetes, by sex, in the registration states of 1910, in 1910 and 1920.

TABLE 12.—*Median Age at Death from Diabetes, by Sex, in the Registration States in 1900, 1910, 1920* *

Year	Both Sexes	Male	Female
1900	57.1	57.4	56.9
1910	59.4	57.9	60.4
1920	60.6	59.5	61.3

* U. S. Census Bureau Mortality Rates, 1910-1920, p. 139.

Averaging the five year experience of the United States for the periods from 1901 to 1905 and from 1911 to 1915 a similar picture is obtained (Table 13), although one which does not show such extreme differences between diabetes death rates of males and those of females, nor such high rates in the later decades of life as have prevailed in New York City.

TABLE 13.—*Death Rates from Diabetes per Hundred Thousand Population by Age Groups and Sex; Annual Averages of 1901-1905, and 1911-1915 in the Registration States of 1900* *

	Both Sexes		Males		Females	
Age	1911-1915	1901-1905	1911-1915	1901-1905	1911-1915	1901-1905
All ages: Adjusted	17.6	12.1	15.7	11.8	19.7	12.3
Crude	19.0	12.7	16.8	12.3	21.3	13.1
Under 5	2.1	2.1	2.2	2.2	1.9	2.0
5 to 9	3.1	3.1	3.0	2.8	3.3	3.4
10 to 14	4.8	4.7	4.2	4.7	5.4	4.7
15 to 19	4.9	3.9	5.1	4.8	4.6	3.0
20 to 24	4.9	3.3	5.6	3.5	4.3	3.1
25 to 34	5.7	5.0	6.1	5.7	5.3	4.3
35 to 44	9.3	7.6	9.2	8.1	9.5	7.1
45 to 54	28.8	19.9	25.4	19.0	32.4	21.0
55 to 64	78.4	50.0	67.2	44.1	89.7	55.9
65 to 74	131.8	80.6	107.6	76.8	154.7	84.3
75 and over	133.0	80.7	123.4	84.8	140.9	77.2

* U. S. Census Bureau Mortality Rates, 1910-1920, p. 87.

The facts before mentioned revealed by mortality statistics are particularly worth bearing in mind, when one recalls the common clinical experience that more men than women are treated for diabetes while more women than men die of this disease, in a standard population unit. This is usually explained by the fact that men more frequently submit themselves to medical examination for insurance and employment purposes, in the interest of the companies concerned or as a measure of health protection for their own sakes.

That changes in death rates from diabetes have been in process in recent years in England, and that important differences prevail between the rates for the two sexes can be readily seen by the following table, taken from the Seventy-Fifth Annual Report of the Registrar-General of England and Wales, Part III, Registration Summary Tables 1901 to 1910, p. 209.

TABLE 14.—*England and Wales: Annual Mortality from Diabetes Mellitus in Successive Decenniums, 1861-1910 per One Million Living at all Ages*

Year	Males	Females	All Persons
1861-1870	43	21	32
1871-1880	54	28	40
1881-1890	74	46	59
1891-1900	90	64	77
1901-1910	104	84	93

In distinction from the experience related in the foregoing for the United States Registration Area, the latest as well as the earliest decade reported for England and Wales shows a higher death rate from diabetes among males than among females, but it is worth noting that in a period of fifty years the death rate of females has increased in 1910 to four times their rate in 1861, while the 1910 rate for males is only 2.4 times their rate of 1861.

ANALYSIS BY RACE

Next to age and sex, race stock is often found to bear directly on susceptibility to a disease, or determine the fatality rate. Diabetes, often called "Judenkrankheit," because of its frequent occurrence among those of Semitic stock, appears to show at least as marked differences in persons of white and colored races and among people of the various nations who make up our population as have been found in tuberculosis.

TABLE 15.—*Adjusted Death Rates from Diabetes per Hundred Thousand Population According to Country of Birth of Mother* *

Country of Birth of Mother	New York State	Pennsylvania	New York City	Chicago	Philadelphia
Ireland	23.8	17.4	26.0	24.8	18.9
Germany (and German Poland)	29.5	21.3	35.3	22.4	20.9
England, Wales and Scotland	19.5	19.2	21.4	....	....
Italy	19.3	9.1	19.7	....	....
United States	15.7	16.4	17.1	19.4	16.2

* U. S. Census Bureau Mortality Rates, 1910-1920, p. 92.

In Table 15 calculations of the Census Bureau are offered, by birth of mother as a basis of race stock, from which it will be seen that in New York City the highest diabetes death rate is found among people of German or Polish stock (preponderantly Jewish). Since the stock other than white, colored or "other" (Chinese, etc.) is not entered on the death certificate, and tabulations have not been made according to religion of the deceased, it is impracticable to use even the most carefully made estimates of Jewish elements in the population of New York City or of other parts of the United States as a wholly reliable basis for calculation of death rates by race from the registrar's records. The deaths from diabetes for the year 1922 in New York City have been

tabulated according to nativity of the deceased, for foreign born whites and for native born of foreign parentage, but the percentage of Jewish persons among people coming from various countries contributing immigrants in large numbers of the United States varies too widely to permit a calculation with reasonable accuracy of the number of Jews in these two groups, to serve as a basis of racial death rates. Table 16 gives the facts as recorded.

The high death rates of 101 for Germans and seventy-five for Austrians indicate more the racial liability of the Jews from these countries living in New York than any special hazard of other races claiming these countries as their birthplace. In certain groups of

TABLE 16.—*Deaths from Diabetes, New York City; Nativity of Deceased and Rates per Hundred Thousand Population of Different Nationalities (Census 1920)*

Birthplace	Nativity of Deceased	
	Deaths	Death Rate
United States: Negroes	31	70
White	536	15
Ireland	106	52
Germany	196	101
Italy	98	25
Russia	203	42
England	28	39
Austria	95	75
Hungary	29	45
Scotland	11	51
British America	10	40
France	12	52
Roumania	21	55
Poland	16	11
Sweden	14	42
Norway	2	8
Denmark	4	44
Other West Indies	3	34
Greece	2	9
Other foreign	31	28
Total	1,448	24.8

Jewish people it is probably true in New York City that the diabetes death rate among them exceeds their tuberculosis death rate.

We can, however, show a very interesting correlation for both New York City and Boston between the increase in the percentage of Jews in the population over a period of years, and the increase in diabetes death rates for the same years in these two cities, in Table 17.

It certainly would seem to be more than an unrelated coincidence that a city of the United States, with more than half of all the Jews of the country, and at present including Jews to the extent of not less than 29.23 per cent. of its population, has shown in the last thirty years a greater increase in diabetes death rates than any other large city in the country and a percentage increase of rate running closely parallel with the percentage of difference in the Jewish element in the population.

TABLE 17.—*Death Rates from Diabetes in Relation to Percentage of Jews in Population*

	New York City		Boston	
	Jews in Population,* per Cent.	Diabetes Death Rate per 100,000 Total Population	Jews in Population,† per Cent.	Diabetes Death Rate per 100,000 Total Population†
1890	11.98	8.0	...	.....
1897	.....	.....	4.3	12.2
1900	17.39	10.0	4.8	12.7
1910	26.28	16.0	8.8	21.4
1913	.....	.....	8.9	21.3
1920	29.23	18.9	...	.....
Percentage of increase...	144	136	107	74

* American Jewish Year Book, 1923-1924; Greater New York 1920, N. Y. C. 1920 Census Committee, p. 888.
† Morrison: Boston M. & S. J. **175**: 54, 1916.

A valuable piece of evidence as to the special hazard of diabetes among the Jews is to be found in a study by Billings [3] of vital statistics of 60,630 persons in selected Jewish families throughout the United States, among whom he shows that of certain important diseases, diabetes had a much higher rate in Jews than among the general population. The ratios calculated from his records show deaths from diabetes to be seven times as common in Jewish males in 1889 as in males in the general population of 1880, with the corresponding ratio for females of 16 to 1.

Until we have reported by physicians cases of diabetes by age, sex, race and occupation on the occasion of establishing a diagnosis, we shall hardly be able to give much more reliable evidence than this of the exact excess liability of Jews to this disease. Any individual clinical experience, however large, can never be free from a certain accidental selection as to source of patients which cannot be trusted to run parallel with the race distribution in the population of the community. We do not know the extent to which what may be a true racial susceptibility affects the death rate from diabetes among the Jews. Sedentary occupations, unsuitable dietary habits, luxurious living, disinclination to indulge in physical exercise, a marked tendency to obesity in men and women among the Jews, particularly after 45 years of age, may well be more definite etiologic factors in the apparent excess of diabetes death rates among the Semitic people than their race.

Among the many variable factors in the study of the influence of race stock, body weight is one which lends itself to exact measurement. For this purpose we have analyzed the weights of a group of 1,429 male industrial workers, all painters, 1,170 of them Jewish, 259 non-Jewish, where age, height and body weight have been recorded accurately in the course of a careful medical examination. In Table 18 the number of

3. U. S. Census Bulletin, No. 19, Dec. 30, 1890.

men in each year, aged from 25 to 55, for which we have the largest number of records, is given, with the sum of the pounds of weight above the normal and those below the normal in each age group, using as normal the weights of the Medico-Actuarial Mortality Investigation, 1912. It appears from this tabulation taking all age groups together, that there is an average of 18.1 pounds overweight among the Jewish painters, and 20.5 pounds overweight among non-Jewish, or viewed in

TABLE 18.—*Number of Men Overweight, from Actuarial Mortality Investigation*

	Jews				Non-Jews			
Age	Number Overweight	Total Pounds Overweight	Number Underweight	Total Pounds Underweight	Number Overweight	Number Pounds Overweight	Number Underweight	Total Pounds Underweight
25	11	207	3	32	4	36	2	15
26	9	120	6	64	1	23	4	58
27	20	351	10	60	4	116	1	18
28	22	364	10	100	4	60	5	47
29	28	480	27	267	5	80	2	14
30	30	513	16	180	5	68	1	18
31	20	356	11	96	5	52	1	10
32	30	485	20	154	5	96	3	24
33	24	485	15	142	5	160	4	32
34	39	711	21	213	8	142	2	26
35	35	680	17	146	5	121	2	8
36	26	479	24	238	8	190	2	23
37	34	574	23	206	3	60	2	14
38	32	680	27	220	4	44	4	40
39	25	574	21	277	6	110	4	88
40	34	663	25	232	7	197	6	149
41	20	456	10	97	2	29	1	18
42	26	366	24	318	2	40	13	213
43	19	397	14	217	3	35	6	96
44	11	118	11	156	6	114	2	31
45	15	337	9	116	4	38	4	65
46	16	285	10	117	5	90	2	17
47	11	282	5	76	3	62	4	53
48	13	153	8	126	4	101	3	38
49	11	167	11	107	1	17	4	47
50	10	191	9	87	3	91	2	60
51	5	95	3	51	2	105	2	25
52	6	91	3	36	2	76	4	25
53	2	13	4	74	..	...	1	15
54	4	61	2	13	2	50	2	38
55	2	28	5	95	1	38	..	..
Total	500	10,702	404	4,313	119	2,449	95	1,325

Average number of pounds overweight: Jews, 18.1; non-Jews, 20.5.
Average number of pounds underweight: Jews, 10.6; non-Jews, 13.9.
Percentage of men overwieght: Jews, 58; non-Jews, 54.
Percentage of men underweight: Jews, 40; non-Jews, 43.

another form, 58 per cent. of the Jews are overweight and 54 per cent. of the non-Jewish. That is, the overweight is not peculiar to the men of Jewish race in this group. Further study of similar records is required before definite conclusions can be reached. Occupation and economic state rather than race would seem from this to be the determining factors in overweight among men.

In a study of 3,100 men and women working in the needle trades (96.7 per cent. of the males and 88.8 per cent. of the females being

Jews), Schereschewsky [4] et al. give data from which the following general statement may be made, namely, that the males in this employed group differ on the average hardly at all in weight, for age and height, from men of the same specifications as found by the Medico-Actuarial Investigation, while the women among the garment workers are, on the average, taking into account age and height, ten pounds heavier than women of similar specifications in the country at large.

Davenport,[5] in the conclusions of his monograph on Body Build and its Inheritance, says "There are geographical differences in build; the heavy build of northern peoples may be due to a physiologic reaction or, in part, to a selective survival of the fleshier individuals or strains.

"The diseases associated with very slender and slender build are: tuberculosis, pneumonia, "nervousness," melancholia. The disease associated with the very fleshy or fleshy build are: diabetes, nephritis and dropsy, apoplexy, and arteriosclerosis and paralysis accompanying it, also numerous diseases of the alimentary tract."

At the other end of the scale of rates from those for the Jewish race, apparently are the negroes, and for these we have a reasonably accurate basis of their population, while among them, owing partly to economic reasons, and partly to lack of education, medical services are apt to be less prompt and less efficient than with other groups of our communities.

The diabetes death rate among negroes is everywhere lower than among the whites of the same region, but it is noticeable that their rate is higher in the cities of the Registration Area and in New York City than in rural areas (Table 19). The difference between rates among the colored and those of the white portion of the population is less in cities than in the rural areas and less in 1920 than in 1910.

In most of the states where rates are reported for white and colored, those for the whites are higher than those for the colored, the most striking contrast being for Florida, with a rate of 11.6 for the white and 3.6 for the colored.[6]

It is not perhaps irrelevant to recall that the highest tuberculosis death rates in the cities of the United States have commonly been found among the negroes and the lowest among the Jews. In diabetes the reverse seems to be the case.

Concepcion,[7] in commenting on the mildness of diabetes among the Filipinos and Japanese where the disease is much more common among

4. Schereschewsky: The Health of Garment Workers, Bull. 71 U. S. P. H. Service, 1915.

5. Davenport: Carnegie Institution of Washington, 1923, December, p. 152, et seq.

6. U. S. Census Bureau Mortality Rates, 1910-1920, p. 89.

7. Concepcion, I.: Incidence of Diabetes Mellitus Among Filipinos, J. Philippine Island M. A. **2**:57 (March) 1922.

TABLE 19.—*Death Rates from Diabetes per Hundred Thousand Population in Registration States, by Race, 1920 and 1910*

Area and Year	Death Rates from Diabetes per 100,000 Estimated Population*			Percentage of Rate for Colored Less Than That for White
	Total	White	Colored	
Registration Area†				
1920	16.1	16.8	7.9	52.9
1910	14.9	15.3	7.0	54.2
Registration States‡				
1920	16.2	16.9	8.0	52.6
1910	15.2	15.5	7.1	54.1
Cities in Registration States‡				
1920	19.4	19.7	13.6	30.9
1910	16.8	17.1	9.7	43.2
Rural Sections of Registration States				
1920	13.1	14.1	5.2	63.1
1910	13.5	13.7	3.2	76.6
Registration Cities in Registration States				
1920	11.4	12.8	7.0	45.3
1910	12.6	13.4	6.9	48.5
All Registration Cities‡				
1920	19.1	19.6	12.7	35.2
1910	16.0	16.4	8.3	49.3
New York City	22.9	23.2	13.7	40.9

* Population estimated by arithmetic method to July of each year based on Federal census of April 15, 1910, and Jan. 1, 1920.
† Exclusive of Hawaii.
‡ Includes District of Columbia.

the males of the population than among the females, suggests that the orientals, particularly the Chinese, stand nervous shock better than occidental races and further that the excessive activity of the latter peoples predisposes to their higher diabetes death rates.

However, he offers little but opinion to support any such thesis and then calls attention to the largely carbohydrate diet of the Filipinos as justifying the expectation of a high diabetes rate among them, without relating the character of the diet to its total caloric content or the estimated need of calories per capita per day under the conditions of occupation, temperature and clothing which prevail among these people.

OCCUPATION

Of the 493 deaths from diabetes in 1922 in New York City for which occupation was recorded, the order of frequency by occupation, as well, as the facts for these by age and sex of the deceased, is given in Table 20.

Due to the fact that the record of deaths from diabetes by occupations in New York City is not uniform with the enumeration of the population by occupations as recorded by the federal census, any calculation of the specific death rates for certain occupational groups is of doubtful reliability and very crude. Tables 20 and 21 present all the information which seems to have any value for the city of New York, so far as death rates for diabetes in various occupational groups is concerned.

The term merchant, which heads the list of occupations with the largest number of deaths, includes all variety of proprietors of merchandizing stores, a great majority of whom in New York City are Jews.

The very crudity of the information in this field of mortality statistics for any community or state of the United States is sufficient

TABLE 20.—*Deaths from Diabetes by Occupation, Sex and Age, New York City, 1922*

Occupation	Total	Sex		Age				
		Male	Female	15 to 24	25 to 34	35 to 44	45 to 64	65 and Over
Merchants	72	70	2	..	..	5	37	30
Clerical	56	46	10	8	7	5	28	8
Laborers	46	46	..	1	3	4	26	12
Personal service	45	30	15	1	3	5	27	9
Clothing workers	42	37	5	1	1	3	28	9
Other trades	40	35	5	4	5	1	19	11
Salesmen	39	29	1	1	1	2	16	10
Railway and boats	15	15	..	1	..	4	7	3
Carpenters	12	12	..	..	2	1	5	4
Newspaper writers	11	11	..	1	1	5	3	1
All building work	9	9	..	..	..	2	6	1
Bartenders	9	9	..	1	..	2	3	3
Bakers	9	9	..	1	1	1	5	1
Teachers	9	3	6	..	..	1	4	4
Printers	8	7	1	..	..	1	4	3
Shoemakers	7	7	..	..	..	..	5	2
Painters	6	6	..	..	1	..	5	..
Clergymen	6	6	..	..	..	..	4	2
Peddlers	5	5	..	..	..	1	2	2
Policemen	5	5	..	..	..	2	2	1
Chauffeurs	5	5	..	..	1	3	..	1
Butchers	5	5	..	..	..	..	2	3
Cigarmakers	5	2	3	1	..	..	4	..
Mechanics	5	5	..	..	..	..	5	..
Managers	4	3	1	..	..	..	3	1
Physicians	4	4	..	..	..	..	3	1
Plumbers	3	3	..	..	..	..	1	2
Bankers	3	3	..	..	..	..	..	3
Undertakers	2	2	..	..	..	..	1	1
Trained nurses	2	..	2	..	..	1	..	1
Lawyers	2	2	..	..	..	..	2	..
Civil employees	2	1	1	..	..	..	1	1
Machinists	2	2	..	..	..	1	1	..
Furriers	2	2	..	..	..	1	1	..
Blacksmiths	1	1	..	..	..	..	1	..
Electrician	1	1	..	..	..	1	..	..
Fireman	1	1	..	..	..	..	1	..
Letter carrier	1	1	..	..	..	..	1	..
Civil engineer	1	1	..	..	..	..	1	..
Street cleaner	..	..	..	..	..	..	..	..
Totals	493	441	52	21	26	52	264	130
Total diabetes deaths recorded in 1922	1,448	581	867					

This does not include thirty-five deaths under 15 nor the deaths of women where occupation was given as that of housewife or other than as specified in the list above (815), nor of 140 men whose occupation was given as other than as specified in list.

reason for calling attention to the few reasonably adequate sources of information on this subject, in the literature of other countries.

The most reliable information is to be found in the supplement to the seventy-fifth Annual Report of the Registrar-General of England and Wales, Part IV, Mortality of Men in Certain Occupations. This report of the registrar's office deals with 132 specified occupations for males, among whom those occupied and retired of all ages from 25 to

65 years, inclusive, were enumerated in the census and among whom deaths have been tabulated by standard causes. Among thirty-one of these occupations or occupational groups the number of deaths from diabetes in all the males of all 132 occupations are represented in the deaths in the thirty-one occupation groups chosen for reporting here.

In Chart 7 will be found arranged in order the comparative mortality figures as calculated in the Registrar's report, those of the thirty-one occupations selected because of showing fifty or more deaths from

TABLE 21.—*Death Rates from Diabetes in the Chief Reported Occupations, New York City, 1922*

Occupation	Number Reported U. S. Census		Estimated Round Numbers		Diabetes Deaths		Death Rate from Diabetes per 100,000	
	Male	Female	Male	Female	Male	Female	Male	Female
Merchants	.....	.....	.....	.....	70	2	..	..
Clerical	137,283	68,949	140,000	70,000	46	10	33	14
Laborers	.....	.....	.....	.....	46	..	..	..
Personal service (entire class)	149,623	156,667	150,000	158,000	30	15	20	9
Laborers, domestic and personal service	1,515	.....	1,600	.....	..	..	..	..
Clothing workers (semi-skilled operators in clothing industries)	67,865	67,817	68,000	68,000	37	5	56	7
Salesmen (in stores)	87,658	.....	90,000	.....	29	1	32	..
Railway and boats	.....	.....	.....	.....	15	..	..	..
Transportation (entire class)	218,368	.....	220,000	.....	..	..	..	..
Carpenters	42,478	.....	44,000	.....	12	..	27	..
Newspaper writers	.....	.....	.....	.....	11	..	..	..
Editors and reporters	3,364	.....	4,000	.....	..	..	..	..
All building work Laborers	22,959	.....	24,000	.....	..	..	..	..
Semiskilled operators	1,292	.....	1,300	.....	..	..	..	..
Apprentices to bldg. tr.	5,076	.....	6,000	.....	..	..	..	..
Bartenders	5,406	.....	5,000	.....	9	..	180	..
Bakers	15,510	.....	16,000	.....	9	..	56	..
Teachers (school)	6,048	27,546	7,000	28,000	3	6	43	21
Printers	8,094	5,428	9,000	6,000	7	1	78	17
Shoemakers	8,062	.....	9,000	.....	7	..	78	..
Painters	25,439	.....	26,000	.....	6	..	23	..
Clergymen	4,037	.....	5,000	.....	6	..	120	..
Peddlers	.....	.....	.....	.....	5	..	..	..
Policemen	11,725	.....	12,000	.....	5	..	52	..
Chauffeurs	49,185	.....	50,000	.....	5	..	10	..
Butchers (in slaughter houses)	1,627	.....	1,700	.....	5	..	..	..
Cigarmakers	7,463	6,012	8,000	7,000	2	3	25	43
Physicians	9,449	.....	10,000	.....	4	..	40	..

diabetes in the three year period, as well as the mortality figure for all males of the population of England and Wales for from 25 to 65 years of age, and for all occupied and retired males of these countries to serve as a level above and below which there are striking variations in mortality figures. Those listed as farmers, etc., do not include agricultural laborers, but constitute the category of farm owners and operators who are not only better off financially but, on the average, about twenty years older than the agricultural laborers who show a maximum number at the age of 25, while the farmers are most numerous at 45.

The agricultural laborers show the lowest age grouping of all the occupations listed.

The category, railway guards, etc., is exclusive of engine drivers who constitute a small and highly selected class.

The category, coach, omnibus service, etc., is exclusive of motor drivers and chauffeurs.

It will be noted that those occupations which in the main receive relatively low return for their labor, and in which a very considerable amount of bodily exercise is necessary, have a mortality figure at or

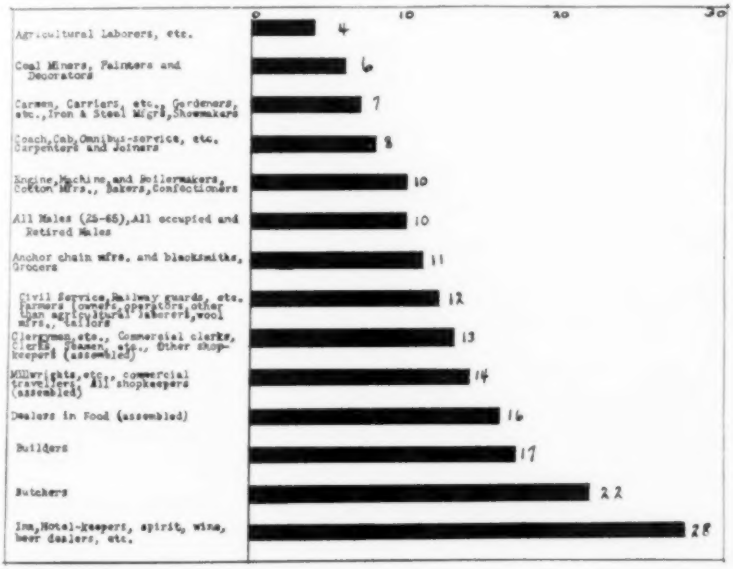

Chart 7.—Comparative mortality figures for diabetes of men between the ages of 25 to 65 years, in certain occupations in England and Wales, 1910-1912; figures to right of columns death rate per hundred thousand.

below the figure for all males of the same ages, whereas most of the occupations showing a higher mortality figure do not require much physical exertion and are relatively better paid.

When the same basic data are presented by the Registrar in what he alludes to as social classes, which are really broad general groups by industries or occupations, not by relative incomes, the mortality figures in Table 23 are found [8] expressed in death rates per hundred thousand.

8. Supplement to the Seventy-Fifth Annual Report of the Registrar-General for England and Wales, Part IV.

TABLE 22.—*Comparative Mortality Figures for Diabetes, Occupied and Retired Males Aged from 25 to 65 Years, by Social Classes, England and Wales, 1910-1921*

I	Upper and middle classes	14
II	Intermediate, excluding unoccupied	14
III	Skilled workmen	9
IV	Intermediate	8
V	Unskilled workmen	8
VI	Textile workers	11
VII	Miners	6
VIII	Agricultural laborers *	4

* Most of these are in a young age group.

The best information on this subject for French experience is presented by Bertillon [9] in his paper on Mortality and the Causes of Death According to Occupation, from which the following is quoted:

Diabetes is very common among the following occupational groups:

1. In the learned professions, especially among lawyers and doctors. Pharmacists and clergymen have lower, though high rates. Lastly, teachers, architects and musicians have average rates.
2. Occupations exposed to alcoholism; inkeepers, brewers and maltsters.
3. Butchers.
4. Certain other professions (dyers, commercial travelers, commercial clerks, railway clerks).

On the other hand, diabetes is very uncommon in the following occupational groups:

1. Coachmen and drivers, notwithstanding they are proverbial drunkards.
2. Hand laborers of all kinds, such as dock laborers, porters, general laborers, although drunkenness is very common among them.
3. Railway workmen (workers on the road bed; guards, porters), but railway clerks and also engineers and firemen rise to or above the average.
4. Persons engaged in agriculture (except farm tenants, who are less favored than domestic servants on the farm), gardeners and farm laborers.
5. Several other manual occupations carried on in the open air (masons, shipbuilders).
6. Miners and quarrymen (except lead miners).

We find only average or insignificant figures in the metal working and textile industries, sedentary occupations, and those pursued on the water.

In the main, the French experience supports the report of the Registrar-General of England, to the effect that those occupations which involve hard manual and bodily labor show low diabetes death rates.

Various writers [10] have expressed themseleves to the effect that occupations involving nervous strain and worry show high prevalence of diabetes.

I am inclined to agree with Kober and Hayhurst (Industrial Health, 1924, p. 972) that such an inference is doubtful, especially when lacking any control information as to race, weight, height, age and dietary

9. Transactions of the Fifteenth International Congress on Hygiene and Demography **1**, Part II, pp. 364-366, 1912.

10. Thompson, W. G.: Occupational Diseases, p. 151. Dublin, L. I.: Causes of Death by Occupation, U. S. Dept. of Labor Bull. 207, 1917.

habits of persons supposed to be suffering a nervous strain because of their occupations. The question of first importance is, whether such persons are not overeating and underexercising, a hygienic sin, particularly common among people of sedentary, highly skilled trade or professional occupations.

Among employees of the B. F. Goodrich Company, rubber manufacturing establishment,[11] and among the steel workers in a Pennsylvania city[12] diabetes for the ages and sexes of the groups concerned does not exceed its incidence in the general population.

Hoogslag[13] says of his 250 cases (ages from 10 to 79) that occupation was an unmistakable factor, in that conditions of work favoring corpulence favored diabetes. "Captains of passenger steamers are peculiarly predisposed, as they have to preside at meals and get little exercise. Lipogenous diabetes is found almost exclusively among the well to do. Diabetes among the thin is found in the rich and poor alike, in children and especially in brain workers and in those with much responsibility."

MARITAL STATE

The marital state of the deceased (single, married, widowed, divorced) in those over 15 years of age, sometimes coincides with distinct differences in death rates, and in Table 23 the death rates by sex for the four usual categories are shown for the city of New York for the year 1922.

TABLE 23.—*Death Rates from Diabetes per Hundred Thousand Population Over 15 Years of Age by Marital State and Sex, New York City, 1922*

	Both Sexes			Male			Female		
Marital State	Population 15 Years and Over	Deaths from Diabetes	Death Rate from Diabetes per 100,000	Population 15 Years and Over	Deaths from Diabetes	Death Rate from Diabetes per 100,000	Population 15 Years and Over	Deaths from Diabetes	Death Rate from Diabetes per 100,000
Single	1,472,967	138	9.4	784,924	73	9.3	688,043	65	9.4
Married	2,228,900	805	34.6	1,178,867	379	32.2	1,150,033	426	37.1
Widowed	342,215	463	13.5	81,432	106	13.0	260,783	357	13.6
Divorced	11,420	7	61.3	4,436	4	90.1	6,984	3	42.9
Not reported	16,993	...	....	12,997	...	....	3,996	...	....
Totals	4,172,495	1,413	33.8	2,062,656	562	27.2	2,109,839	851	40.3

Since we have not the ages of the persons whose deaths are here tabulated by marital state, speculation is idle as to the causative factors in these differences, and where the rates are astonishingly high, as among the divorced, the numbers of deaths, four for males and three

11. U. S. P. H. Report No. 50, **37**:3083 (Dec. 15) 1922.
12. U. S. P. H. Report No. 53, **35**, Dec. 31, 1920.
13. Hoogslag, W.: Nederlandsch. Tijdschr. v. Geneesk. **2**:1934 (Oct. 28) 1922.

for females, are too small to justify any discussion. It may be that among divorced persons self-indulgence and the financial means to satisfy it are commoner than among other groups of the adult population.

SEASONAL VARIATION

The seasonal variation in the death rates of diabetes follows very closely the curve so generally observed in the cities and states of the northeastern United States for deaths from diseases of the respiratory

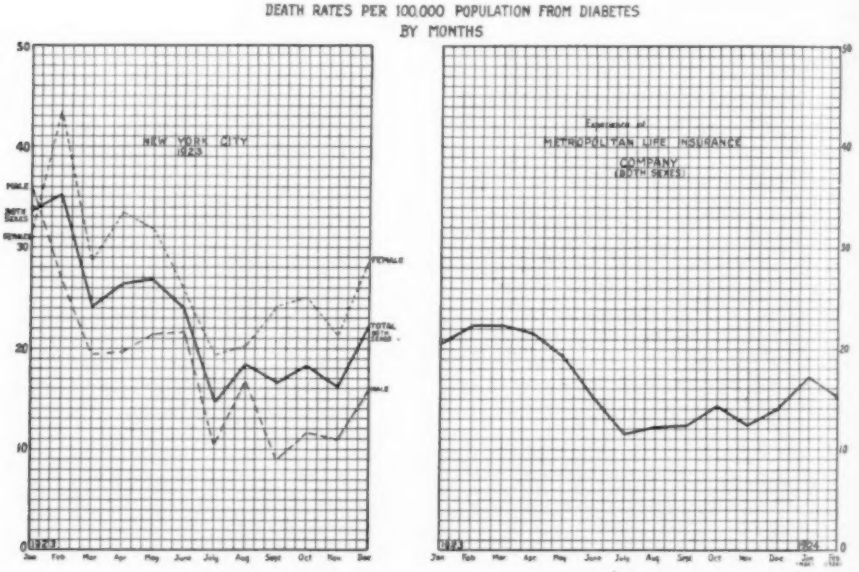

Chart 8.—Seasonal variation in death rates from diabetes

tract. Diabetes shows its highest death rates from January to May and its lowest rate in July among both men and women, in the population of New York City (1923), and among the industrial policy holders of the Metropolitan Life Insurance Company (for 1923, and two months of 1924) as can be seen in Chart 8 and Table 24.

While the intercurrent affections which have a similar seasonal variation in distribution may be wholly responsible for the month of death of diabetic patients, the temperature of the months in which the climate of New York imposes the smaller demands or burden on the heat production or food intake of the body may be the reason for the low death rate, regardless of the lower incidence of respiratory tract

TABLE 24.—*Deaths and Death Rates per Hundred Thousand Population from Diabetes by Months, 1923*

Months, 1923	New York City						Industrial Experience Metropolitan Life Ins. Co.	
	Deaths			Death Rates				
	Total	Male	Female	Total	Male	Female	Deaths	Death Rates
January	169	91	78	33.5	36.1	30.9	230	20.3
February	160	61	99	35.2	26.8	43.6	229	22.3
March	121	49	72	24.1	19.4	28.6	256	22.3
April	129	48	81	26.4	19.6	33.5	243	21.6
May	134	54	80	26.7	21.4	31.8	226	19.2
June	116	53	63	23.8	21.6	25.8	173	15.1
July	74	26	48	14.6	10.3	19.4	137	11.5
August	96	42	54	18.4	16.8	20.3	145	12.1
September	81	22	59	16.6	9.0	24.2	143	12.2
October	92	29	63	18.2	11.6	25.0	174	14.3
November	79	27	52	16.1	11.4	21.4	149	12.5
December	112	40	72	22.2	15.9	28.6	174	14.1
Total (1923)	1,360	512	848	22.9	17.1	28.3	2,279	16.1
1924								
January							213	17.2
February							178	15.2

infections so usual between June and November. That there is a distinct seasonal liability to death among diabetic patients in the winter months cannot be doubted, whatever may be the cause.

GEOGRAPHICAL DISTRIBUTION

If we compare the death rates from diabetes in New York City with rates for the same years in other large cities of the United States we find not only wide variation in the rates in the several cities for any one year, but remarkable differences in the percentage of increase in the rates over a period of twenty-one years as recorded in Table 25.

TABLE 25.—*Death Rates from Diabetes per Hundred Thousand Population in Twenty Large Cities of the United States*

Cities	1900	1905	1910	1915	1920	1921	Average of Rates 1900-21	Per Cent. of Increase 1900-21
Baltimore	8.2	11.6	18.0	17.8	20.6	22.1	10.8	169
Boston	15.2	17.3	20.8	27.1	24.2	19.8	19.9	30
Buffalo	12.8	16.7	18.1	23.7	23.5	22.3	19.0	74
Camden	4.0	6.0	14.7	9.4	14.5	20.1	10.7	402
Chicago	6.7	11.4	15.8	17.6	20.4	20.3	14.4	203
Cleveland	4.4	7.6	13.3	16.5	17.2	17.1	12.2	288
Denver	12.7	12.3	11.7	18.2	19.7	15.6	14.3	23
Indianapolis	11.8	11.6	18.7	20.4	19.5	19.0	15.2	61
Kansas City, Mo.	4.3	8.9	11.2	15.6	13.4	18.7	11.2	335
Los Angeles	11.7	15.3	14.5	19.3	16.8	23.4	15.8	100
Minneapolis	6.4	12.7	10.6	17.4	23.1	20.9	13.5	226
Newark	13.4	17.3	21.8	20.3	22.7	18.4	17.4	37
New Haven	17.6	6.4	18.6	20.8	27.4	28.1	20.6	59
New Orleans	3.5	16.4	8.5	15.6	15.7	19.8	11.1	465
New York	11.4	11.7	18.7	24.1	23.4	24.1	18.7	111
Paterson	6.7	13.9	24.6	23.6	20.5	24.0	15.7	258
Philadelphia	8.4	19.2	16.1	18.7	18.1	19.1	14.7	127
San Francisco	14.3	10.4	21.7	25.2	21.9	25.0	21.1	75
St. Louis	5.7	15.4	12.9	18.7	16.1	21.1	13.9	270
Washington	7.5		16.5	18.5	15.1	17.4	15.3	132

The cities which have had death rates from diabetes of over ten per 100,000 of population throughout the twenty-one years (from 1900 to 1921) show uniformly a lower percentage of increase in rate than do the cities which in 1920 had rates below ten, only Los Angeles and New York showing increases of 100 per cent. or over among the high rate cities, the others showing percentages of increases of 127 to 465 per cent.

TABLE 26.—*Death Rates from Diabetes per Hundred Thousand Population by States*

	Average Rates 1900-1921		Rate 1921
New Hampshire	20.2	New Hampshire	29.0
Vermont	20.1	Maine	26.0
Nebraska	20.1	Vermont	24.7
Oregon	19.2	New York	23.4
Rhode Island	18.7	Connecticut	22.2
New York	18.4	Oregon	21.2
Connecticut	18.4	California	20.3
Maine	18.4	Massachusetts	20.2
Massachusetts	18.1	New Jersey	19.7
Illinois	17.1	Rhode Island	19.7
California	16.6	Nebraska	19.5
Kansas	16.2	Minnesota	18.1
Ohio	15.8	Illinois	18.0
Wisconsin	15.4	Ohio	18.0
New Jersey	14.8	Wisconsin	17.5
Minnesota	14.8	Pennsylvania	17.3
Michigan	14.2	Maryland	17.1
Pennsylvania	13.9	Michigan	16.5
Missouri	13.8	Indiana	16.3
Maryland	13.6	Missouri	15.9
Indiana	13.4	Kansas	15.6
Washington	13.2	Washington	15.1
Utah	12.7	Delaware	14.6
Delaware	12.2	Colorado	14.3
Montana	11.4	Utah	14.3
Colorado	11.1	Florida	10.4
Virginia	8.9	Virginia	10.1
Florida	8.8	Montana	9.9
Kentucky	8.1	Louisiana	9.4
South Dakota	7.8	Kentucky	8.7
Louisiana	7.5	North Carolina	7.5
North Carolina	7.5	South Carolina	7.3
Tennessee	6.5	Tennessee	6.1
South Carolina	6.1	Mississippi	5.8
Mississippi	5.5	South Dakota not reported	
United States	14.29	United States	16.8

There is shown a tendency to greater uniformity of rates among these large cities at the 1921 higher rates than was the case in 1900. In 1900 only nine of the twenty cities had a diabetes death rate of over ten per 100,000 population, four having rates between three and five and no city a rate as high as eighteen. In 1921 all twenty cities showed rates of at least ten and five cities had rates of over eighteen per 100,000 of population.

The variation of death rates from diabetes among the thirty-five registration states during the years 1900 to 1921 and for the year 1921, arranged in order of descending rate, is seen in Table 26 and the graphic representation of these differences in 1921 in Chart 9.

Three factors, capable of fairly exact expression which may throw light on the reasons for these variations, are the percentage of population of a state living at 45 years of age or over, in 1920,[14] the expectancy of life for the population of a state calculated for the end of the first

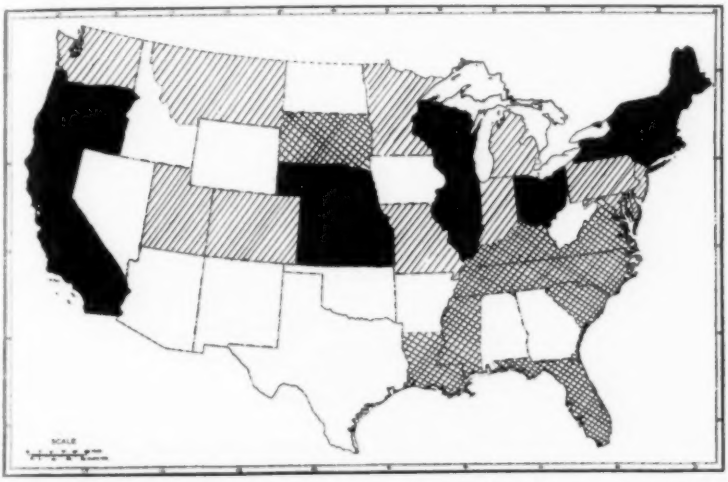

Chart 9.—Average death rates from diabetes, 1900-1921, by states; solid black, average of rates, 1900-1921, over fifteen per hundred thousand; parallel lines, average of rates, 1900-1921, from ten to fifteen per hundred thousand; crossed lines, average of rates, 1900-1921, below ten per hundred thousand, and white, no record.

TABLE 27.—*Percentage of Population Forty-Five Years and Over in United States Registration States, 1920*

	Per Cent.		Per Cent.
Vermont	28.5	Colorado	21.9
New Hampshire	28.5	Michigan	21.7
Maine	28.1	Illinois	21.6
California	26.1	New Jersey	21.1
Indiana	24.8	Pennsylvania	20.9
Oregon	24.4	Minnesota	20.7
Massachusetts	24.2	Nebraska	20.5
Delaware	23.7	Kentucky	19.9
Rhode Island	23.3	Florida	19.4
Ohio	23.2	Tennessee	18.6
Missouri	23.1	Virginia	18.5
Washington	22.7	Montana	18.4
New York	22.5	Utah	16.6
Kansas	22.4	Mississippi	16.3
Maryland	22.3	North Carolina	16.1
Connecticut	22.2	Louisiana	16.1
Wisconsin	22.1	South Carolina	14.4

year of life, in 1920,[15] and the per capita income of the population of a state in 1919.[16]

These facts are presented in Tables 27, 28 and 29.

14. U. S. Bureau of Census Report, **3**, 1920.
15. United States Life Tables, 1921.
16. Income in the United States, 1909-1919, National Bureau Economic Research.

TABLE 28.—*Per Capita Income of States, 1919*

State	Per Capita Income 1919	Death Rate from Diabetes per 100,000, 1919	State	Per Capita Income 1919	Death Rate from Diabetes per 100,000, 1919
United States	$627	....	New Hampshire	$597	16.0
District of Columbia	884	17.8	Maine	583	20.9
New York	874	21.2	Indiana	581	16.5
Nevada	850	....	Minnesota	581	13.6
California	820	17.3	Wisconsin	557	15.1
Delaware	792	11.3	Texas	538	....
Wyoming	789	....	Missouri	535	13.9
Massachusetts	788	19.5	Oklahoma	534	....
Washington	786	15.4	Vermont	529	24.7
Illinois	765	15.9	Utah	517	11.2
New Jersey	758	17.4	North Dakota	515	....
Rhode Island	720	24.5	Montana	512	10.0
Connecticut	717	19.5	West Virginia	448	....
Oregon	711	21.1	South Carolina	437	6.0
Iowa	706	....	Louisiana	429	6.6
Michigan	704	15.7	Virginia	429	8.4
Nebraska	702	20.7	Florida	420	7.2
Ohio	689	16.5	New Mexico	408	....
Maryland	689	16.2	Georgia	394	....
South Dakota	685	....	Kentucky	392	7.8
Pennsylvania	683	14.5	North Carolina	383	6.2
Arizona	664	....	Arkansas	379	....
Colorado	639	10.8	Tennessee	365	6.6
Idaho	604	....	Mississippi	351	5.0
Kansas	602	15.2	Alabama	345	....

TABLE 29.—*Death Rate from Diabetes by States, Related to Age and Economic Factors*

State	Death Rates from Diabetes		Per Cent. of Population 45 Years and Over	Per Capita Income 1919	Expectancy of Life in First Year, 1920	
	1920	Av. 1900-21			Male	Female
New Hampshire	23.4	20.2	28.5	$597	.....	.....
New York	23.3	18.4	22.5	874	57.13	59.16
Maine	21.8	18.4	28.1	583	.....	.....
Connecticut	21.1	18.4	22.2	717	58.45	60.33
Massachusetts	20.9	18.1	24.2	788	58.98	60.32
Nebraska	20.7	20.1	20.5	702	.....	.....
Rhode Island	20.2	18.7	23.3	720	.....	.....
Vermont	19.6	20.0	28.5	529	.....	.....
Wisconsin	18.7	15.4	22.1	557	62.77	63.55
New Jersey	18.6	14.8	21.1	758	58.02	59.83
Illinois	17.9	17.1	21.6	765	59.19	60.81
Ohio	17.6	15.9	23.2	689	60.11	61.39
Oregon	17.5	19.2	24.4	711	60.73	62.30
Minnesota	17.3	14.8	20.7	581	61.86	62.97
California	17.1	16.6	26.1	820	57.75	61.12
Maryland	17.0	13.6	22.3	689	58.42	59.77
Kansas	16.6	16.2	22.4	602	63.14	63.48
Indiana	16.5	13.4	24.8	581	60.90	60.51
Michigan	16.3	14.2	21.7	704	59.76	59.48
Pennsylvania	16.3	13.9	20.9	683	57.93	59.68
Colorado	14.5	11.1	21.9	639	.....	.....
Washington	13.9	13.2	22.7	786	60.70	62.60
Utah	13.2	12.7	16.6	517	58.77	61.18
Missouri	12.1	13.8	23.1	535	60.32	61.56
Montana	10.8	11.4	18.4	512	.....	.....
Delaware	10.7	12.2	23.7	792	.....	.....
Virginia	9.3	8.9	18.5	429	60.75	61.22
Florida	8.8	8.8	19.4	420	.....	.....
South Dakota	....	7.8	18.0	685	.....	.....
Louisiana	7.8	7.5	16.1	429	.....	.....
North Carolina	7.7	7.5	16.1	388	61.25	60.72
Kentucky	7.5	8.1	19.9	392	60.97	60.05
Tennessee	6.2	6.5	18.6	365	61.54	60.77
South Carolina	6.2	6.1	14.4	437	59.54	60.40
Mississippi	5.8	5.5	16.3	351	.....	.....
United States	16.1†	14.29†	20.8*	627	59.38‡	60.63‡

* Continental United States.
† Registration states.
‡ Aggregate of states listed, 78 per cent. of total population.

It will be seen that the high rates fall commonly in the states where either high age grouping of the population or high per capita income, or both are present. Where high expectancy of life is recorded for a state (1920) there is commonly a lower diabetes death rate than in states where life expectancy is shorter.

Concepcion [7] gives evidence of an irregular but considerable rise in diabetes mortality rates per 100,000 population in Manila, and relates this in a measure to the increase in per capita sugar consumption expressed in kilograms.

De Langen and Schut [17] say they find in Batavia that diabetes is particularly frequent among the idle rich.

Gajewski [18] reports from the Preuss. Statis. Landesamt. the gradual increase in death rates from diabetes until 1914 up to 9.54 the drop during the war years to 5.9 in 1918, the fall in the rate among

TABLE 30.—*Incidence of Diabetes Mellitus Among Filipinos*

Year	Death Rate from Diabetes per 100,000	Per Capita Sugar Consumption, Kilograms
1910	2.3	3.19
1911	0.9	11.09
1912	3.3	8.15
1913	0.8	17.46
1914	1.7	14.69
1915	2.1	18.18
1916	2.5	3.80
1917	3.8	17.90
1918	2.9	15.23
1919	4.2	26.19
1920	4.1	22.79

the women being greater than among the men, and the rise to 6.59 in 1921. These rates, taken together with original information copied directly from the official records in Berlin, are shown in Table 32, giving the experience for males and females in both urban and rural populations of Prussia for the years from 1906 to 1921.

Gajewski noted that where excess nutrition was prevalent before the war the diabetes death rate was highest, and that this rate fell less where food shortage during the war was slight than where there was serious privation.

The food shortage expressed itself not so much in the lack of sugar and carbohydrates as in lack of fats, which should make one suspect that it is not the quality but the gross quantity of food (calories) that plays the chief part in development of a high diabetes death rate in a community where more food is eaten than is required.

17. De Langen and Schut: Medelingen Borgelijken Genees. Diente in Nederland. Indie. **3**:63, 1918.

18. Gajewski, W.: Zur Sterblickeit au Zuckerkrankheit in Preussen seit 1891 nebst Anhang: die Eigensterblickheit der jüdischen Bevölkerung au Zuckerkrankheit im Jahre 1920., Med-statist. Nachr. **11**, III and IV, 1920.

TABLE 31.—*Diabetes Death Rates per Hundred Thousand Population in Prussia, by Years, Rural and Urban Distribution and Sex, 1906-1921*

	Urban			Rural			Whole Country		
Year	Male	Female	Both Sexes	Male	Female	Both Sexes	Male	Female	Both Sexes
1906	11.97	8.62	10.28	3.98	2.88	3.42	7.57	5.49	6.52
1907	12.84	8.67	10.73	4.37	3.29	3.83	8.21	5.75	7.06
1908	13.92	9.74	11.83	4.62	3.45	4.03	8.84	6.32	7.56
1909	13.84	9.64	11.67	4.51	3.38	3.95	8.73	6.24	7.44
1910	15.06	10.49	12.74	4.59	3.41	4.01	9.33	6.33	7.98
1911	14.43	10.52	12.42	5.14	3.85	4.49	9.48	7.03	8.23
1912	14.41	10.71	12.51	5.25	4.37	4.82	9.56	7.44	8.48
1913	15.18	10.91	12.75 (13.0)*	5.76	4.67	5.21	10.23	7.69	8.96
1914	16.39	11.91	13.86 (14.1)*	5.97	4.97	5.22	10.97	8.09	9.54
1915	.....	.....	12.1 *	....	....	4.9 *	9.6 *	7.2 *	8.4 *
1916	.....	.....	11.3 *	....	....	4.5 *	8.8 *	6.7 *	7.8 *
1917	11.68	7.88	9.72	5.23	3.98	4.41	8.32	5.68	6.97
1918	.....	.....	8.1 *	....	....	3.9 *	7.3 *	4.7 *	5.9 *
1919	9.93	6.57	8.14	4.77	3.27	3.99	7.23	4.88	6.02
1920	9.87	6.73	8.23	4.63	3.56	4.06	7.21	5.17	6.14
1921	10.27	8.04	9.16	3.93	3.57	3.75	7.22	5.99	6.59

* Rates taken from Gajewski: Zur Sterblichkeit an Zucker Krankheit in Preussen.

Through the courtesy of the office of the Surgeon-General of the Army, an interesting set of facts is offered with regard to the ratio of diabetes among drafted men ("Defects Found in Drafted Men") from the various states and regions of the United States. Tables 32, 33, 34, 35, 36 and 37 dealing with drafted men are based on the examination of approximately 2,000,000 of the 2,700,000 selective service men who were entrained for camps, and 549,099 who were rejected by the local boards as physically or mentally unfit for all forms of military service. Of this number 740 were found to have diabetes, and of these 725 were rejected as physically unfit for military service.

TABLE 32.—*Diabetes in Drafted Men*

State	No. of Cases	Ratio per 1,000	State	No. of Cases	Ratio per 1,000
Connecticut	44	1.23	Mississippi	10	0.27
Vermont	6	0.71	Virginia	14	0.25
Oregon	11	0.69	Washington	9	0.25
South Dakota	13	0.63	Minnesota	17	0.24
Maine	11	0.55	Missouri	20	0.23
Wisconsin	35	0.55	Ohio	33	0.23
Iowa	34	0.50	Montana	6	0.22
Arizona	4	0.48	North Dakota	4	0.22
Utah	5	0.42	Pennsylvania	45	0.22
Nebraska	12	0.41	Colorado	4	0.18
Maryland	15	0.40	Indiana	13	0.18
New York	101	0.39	Kansas	7	0.18
California	31	0.38	Idaho	2	0.16
District of Columbia	4	0.35	North Carolina	9	0.16
New Hampshire	3	0.35	Tennessee	9	0.15
Rhode Island	5	0.34	Wyoming	1	0.15
Illinois	57	0.32	Alabama	7	0.14
Massachusetts	29	0.32	Oklahoma	7	0.12
Nevada	1	0.30	Texas	12	0.10
New Jersey	22	0.29	Arkansas	4	0.09
West Virginia	11	0.28	Kentucky	6	0.09
Michigan	27	0.27	Florida	2	0.08
South Carolina	3	0.08	Delaware	..	....
Georgia	4	0.06	New Mexico	..	....
Louisiana	1	0.02	State not specified	10	0.11
Alaska	..	....			
Total				740	0.27

TABLE 33.—*Diabetes Mellitus Distribution by Urban and Rural Communities*

	Number of Cases	Ratio per 1,000
Urban	315	0.22
Rural	425	0.20
New York City	61	0.43
Boston	6	0.30
Philadelphia	18	0.38
Chicago	31	0.38

TABLE 34.—*Diabetes Mellitus*

Groups	Total Cases	Ratio per 1,000	Groups	Total Cases	Ratio per 1,000
Agricultural, native white, North, 75% plus	48	0.45	Mountain whites	12	0.16
Agricultural, foreign and native white	115	0.39	Indian, sparsely settled	5	0.16
Agricultural, native white, South	63	0.15	Mexican, sparsely settled	5	0.18
Agricultural, negro, 45% plus	23	0.13	Native white, Scotch origin	4	0.07
Eastern, manufacturing	110	0.49	Russian 10%	4	0.11
Commuters	23	0.31	Scandinavian, 10%	65	0 41
Mining	17	0.18	Finns, 10%	2	0.15
Sparsely settled, 3 or less per square mile	9	0.20	French Canadians, 10% plus	54	0.37
Desert	4	0 33	German and Scandinavian each 10% plus	49	0.50
Maritime	5	0.25	German and Austrian, 20% plus	24	0.24
Mountain	14	0.27	German and Austrian, 15% plus	125	0.36

TABLE 35.—*Diabetes Mellitus, April 1, 1917, to Dec. 31, 1919, Ratio per Thousand per Annum*

By Race and Rank	Admissions		Deaths		Discharges		Days Lost	
	Abs. No.	Rate	Abs. No.	Rate	Abs. No.	Rate	Abs. No.	Noneffective
Total	718	0.17	104	0.03	330	0 08	39.062	0.03
Officers	83	0.40	6	0.03	14	0.07	5,453	0.07
White enlisted	586	0.16	78	0.02	294	0.08	30.875	0.02
Colored enlisted	36	0.13	16	0.06	13	0.05	2,236	0.02
Color not stated	10	....	3	....	8	....	409	....
Native troops	3	0.08	1	0.03	1	0.03	89	0.01
Filipino	1	0.05	0	....	0	....	47	0.01
Hawaiian	1	0 18	0	....	1	0.18	0	....
Porto Rican	1	0.06	1	0.08	0	....	42	0.01
By country where serving:								
United States	501	0.22	73	0.03	264	0.12	23,379	0.03
Europe	196	0.12	28	0.02	59	0.04	14,695	0.02
Other countries	21	....	3	....	7	....	988	....

There are also presented the ratios of diabetes per 1,000 men per annum among the military personnel during the World War, and among the enlisted personnel of the Army for the decade of 1913 to 1922. The reader must be on his guard against comparing these ratios, which are based on incidence and admissions to sick call, with the death rates per 100,000 of population used very generally through the remainder of this study.

These records are of interest chiefly because of the wide geographic distribution of the basic material and the uniformity of examination, procedure and manner of life of the great mass of the men studied during the army experience. It is a matter of particular interest that the admission rates for diabetes for the ten years from 1913 to 1922

TABLE 36.—*Admissions, Enlisted Men, Serving in the United States or Europe by States or Nativity; Ratio of Diabetes Mellitus per Thousand per Annum, April 1, 1917, to Dec. 31, 1919*

Alaska	0	....	Nebraska	13	0.30
Alabama	12	0.18	Nevada	2	0.41
Arizona	0	....	New Hampshire	2	0.15
Arkansas	6	0.10	New Jersey	4	0.04
California	8	0.08	New Mexico	1	0.08
Colorado	4	0.12	New York	61	0.18
Connecticut	5	0.11	North Carolina	14	0.21
Delaware	3	0.42	North Dakota	2	0.08
District of Columbia	1	0.06	Ohio	32	0.17
Florida	4	0.13	Oklahoma	4	0.05
Georgia	11	0.14	Oregon	5	0.18
Idaho	1	0.06	Pennsylvania	41	0.15
Illinois	44	0.19	Rhode Island	5	0.29
Indiana	16	0.17	South Carolina	9	0.19
Iowa	16	0.17	South Dakota	4	0.14
Kansas	15	0.25	Tennessee	6	0.08
Kentucky	10	0.14	Texas	15	0.10
Louisiana	10	0.17	Utah	0	....
Maine	1	0.04	Vermont	5	0.50
Maryland	6	0.13	Virginia	20	0.30
Massachusetts	14	0.12	Washington	1	0.02
Michigan	16	0.13	West Virginia	2	0.04
Minnesota	12	0.13	Wisconsin	14	0.15
Mississippi	14	0.29	Wyoming	1	0.09
Missouri	25	0.21	Others	89	....
Montana	2	0.06			
Total				608	0.17

TABLE 37.—*Diabetes Mellitus, U. S. Army, Enlisted Men; Admissions Ratios per Thousand per Annum*

	White				Colored		Native	
	U.S.	P. I.	Hawaii	Panama	U. S	P. I.	Scouts	P. R.
1913	0.21	0.11	....	1.25	....	....	....	....
1914	0.15	....	....	....	....	....	....	....
1915	0.21	....	....	....	....	....	....	....
1916	0.18	0.19	....	0.29	1.21	....	....	....
1917	0.18	0.11	....	0.25	0.08	....	....	....
1918	0.20	0.18	0.18	0.12	0.16	....	0.17	0.12
1919	0.23	0.26	....	....	0.15	....	....	....
1920	0.16	0.11	....	0.45	....	....	0.14	....
1921	0.10	....	0.15	....	0.32	....	....	....
1922	0.16	....	0.20	0.15	....	....	....	0.37

show such slight variations, while the rates for every city and state of the United States have during the same period increased with great uniformity for males over 20 years of age. Obesity and physical indolence are discouraged by the hygiene and necessities of army life, whether in war or in peace.

DEATH RATES FROM DIABETES IN RELATION TO VARIATION IN PER CAPITA CONSUMPTION OF FOOD, PARTICULARLY SUGAR

That the general dietetic habits of people vary widely as measured in calories, and have changed in the direction of a greater liberality of food intake in recent times, must be admitted if we accept the statements of Taylor, Legendre and others on this subject. According to

Taylor,[19] the prewar daily per capita consumption of food in Italy was 2,560 calories, in the United Kingdom 2,860, in Germany 3,200 and in the United States 3,650. Legendre[20] estimates that the average per capita daily consumption of food in France has risen from 1,645 calories in 1832 to 2,255 in 1862, and to 3,160 calories in 1912.

Taylor notes with regard to the United States that possibly 10 per cent. of the population consumes over 4,000 calories a day without work requirements to justify this intake, and that of the industrially submerged tenth, perhaps from 5 to 10 per cent. consume less than 2,000 calories a day, and he lays down the general principle that the work of prosperity increases food consumption and the idleness of hard times reduces it.

It is reported by the Bureau of Animal Industry of the U. S. Department of Agriculture that the annual per capita consumption of meat has fallen in the last fifteen years from 179 to 155 pounds, this reduction having been replaced by an increase in the use of cereals, sugar, milk and fruits. In contrast with this change in the United States is the reported annual consumption of 250 pounds of meat per capita in Australia.

Taylor estimates that with our present food habits, which include the annual consumption of about 100 pounds of sugar per capita, we provide 500 calories a day in our average ration of 3,600 calories for all ages from sugar which we not only like particularly but find a cheap food and most effective for workers.

In spite of the probability that with normal conditions of economic life no great expansion occurs in national food consumption expressed in calories as Taylor states, it is, however, probable that among certain racial, economic and age groups prosperity tends to tempt them into food habits which exaggerate the usual discrepancy between the amount of food intake and the quantity needed for their respective heat, growth, repair and work requirements.

One index of the tendency of our people to use larger amounts of food is the record of per capita consumption of sugar, which is offered here not as an explanation of the increased death rates from diabetes in recent years, but more as a sign of the tendency to excesses in the use of foods of all kinds, beyond the needs of persons for foods in proportion to their expenditure of energy at the different ages of life, and in particular in the later decades.

The estimated per capita consumption of sugar per annum over certain years in the United States, Great Britain and France, and the diabetes death rates for the Registration Area of the United States, for

19. Taylor, A. E.: J. of Home Economics **16**:55 (Feb.) 1924; Harvard Economic Rev. **2**:283 (April) 1924.

20. Legendre: Bull. Soc. scient. d'Hyg. **11**:161, 1923.

Great Britain and for Paris (not available for France), for some of the same years is shown in Chart 10 and in Tables 38, 39 and 40.[21]

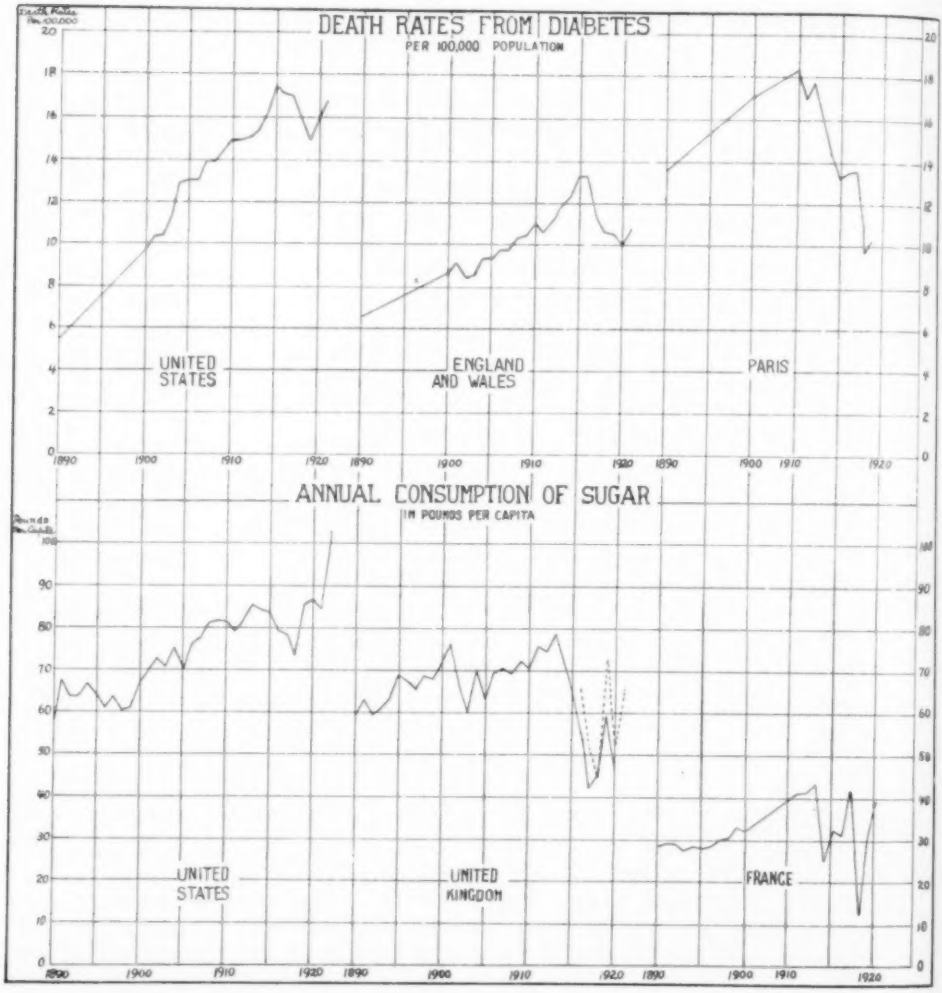

Chart 10.—The estimated per capita consumption for sugar for certain years in the United States, Great Britain and France, and the diabetes death rates for the United States, Great Britain and Paris for the same years.

21. Tables of sugar consumption are based on various government and trade reports, including Yearbook of U. S. Department of Agriculture, General Statistics of France, International Sugar Trade Journal, Concerning Sugar by Palmer, and Licht's reports.

TABLE 38.—*Sugar Consumption in Relation to the Diabetes Death Rates in United States*

Year	Diabetes Death Rate* per 100,000	Sugar Consumption in Pounds per Capita	Year	Diabetes Death Rate* per 100,000	Sugar Consumption in Pounds per Capita
1890	5.5	54.46	1907	13.9	77.54
1891	....	67.46	1908	13.9	81.17
1892	....	63.70	1909	14.4	81.80
1893	....	63.83	1910	14.9	81.60
1894	....	66.64	1911	14.9	79.20
1895	....	64.23	1912	15.0	81.30
1896	....	60.90	1913	15.3	85.40
1897	....	63.50	1914	16.2	84.29
1898	....	60.30	1915	17.5	83.83
1899	....	61.00	1916	17.1	79.34
1900	9.7	66.60	1917	17.0	78.58
1901	10.3	69.70	1918	15.9	73.36
1902	10.4	72.80	1919	14.9	85.43
1903	11.3	70.90	1920	16.1	86 56
1904	12.9	73.30	1921	16.8	84.47
1905	13.0	70.50	1922	....	103.18
1906	13.0	76.10			

* Diabetes death rates from Joslin. Rate for 1890 is for census year, others for calendar year.

TABLE 39.—*Sugar Consumption in Relation to Diabetes Death Rate in Great Britain*

Year	Diabetes Death Rate* per 100,000	Sugar Consumption in Pounds per Capita	Year	Diabetes Death Rate* per 100,000	Sugar Consumption in Pounds per Capita
1890	6.5	58.80	1906	9.7	69.35
1891	....	63.00	1907	9.7	70.76
1892	....	59.60	1908	10.3	69.49
1893	....	60.88	1909	10.4	72.40
1894	....	63.16	1910	11.0	70.30
1895	....	68.85	1911	10.6	75.93
1896	....	67.07	1912	11.1	74 69
1897	....	65.19	1913	11.8	78.53
1898	....	68.74	1914	12.2	72.39
1899	....	68.42	1915	13.2	65.26
1900	8.6	71.60	1916	13.2	56.28
1901	9.1	76.33	1917	11.3	42.11
1902	8.4	66.47	1918	10.6	45.70
1903	8.5	60.29	1919	10.5	59.64
1904	9.3	70.35	1920	10.0	45.04
1905	9.3	63.34	1921	10.8	.....

* Diabetic rates from Joslin for England and Wales.

TABLE 40.—*Sugar Consumption in Relation to the Diabetes Death Rate in France*

Year	Diabetes Death Rate per 100.000, Paris	Sugar Consumption in Pounds per Capita, France	Year	Diabetes Death Rate per 100 000, Paris	Sugar Consumption in Pounds per Capita, France
1890	13.5	28.9	1910	18.4	40.11
1891	....	29.46	1911	16.9	41.09
1892	....	29.28	1912	17.7	41.48
1893	....	27.89	1913	16.0	43.84
1894	....	28.62	1914	14.3	25.86
1895	....	28.20	1915	13.2	39.83
1896	....	28.80	1916	13.4	31.68
1897	....	30.09	1917	13.5	41.07
1898	....	30.57	1918	9.6	13.28
1899	....	33.34	1919	10.3	31.11
1900	17.0	32.49	1920	....	39.28

It is apparent that rises and falls in the sugar consumption are followed with fair regularity within a few months by similar rises and falls in the death rates from diabetes, the changes during the period of the World War being particularly striking. If we had the death rate for diabetes of France as we have for the United States and Great Britain we should in all probability find a lower rate than prevailed in the latter countries, as the high rate of Paris is not so high as the rates have been over the same period for New York and London. The Paris rates are used because they are the only ones available for comparison with the sugar consumption of France, since it is the practice of the office of vital statistics of France to include diabetes in a group of general diseases in an abbreviated classification of causes of deaths under thirty-eight titles, instead of publishing by age, sex and cause, reports of deaths for the country as a whole for the 189 titles as is usual in England and the United States.

Riesman [22] after pointing out the fact that urine tests have changed so little in the last twenty to thirty years that greater accuracy in diagnosis of diabetes has probably not occurred during that time, expresses his opinion that the cause of the true increase of diabetes is the greater per capita sugar consumption, coupled with the increase of sedentary habits among most classes of people.

Joslin has given the impression in discussion of the substance of this paper that the increase in the per capita consumption of sugar in the United States can be discounted as a probable factor in the increase of diabetes death rates because of a presumed reduction in the per capita annual consumption of apples. Even if he can offer satisfactory evidence that there has been a bona fide reduction in apple consumption during the period of rising use of sugar, he would still have to meet the facts which Taylor mentions that there has been coincident with the reduction of per capita use of meat an increase in the use of fruits. Many other fruits besides apples carry a high sucrose content, and there is much evidence to show that increase in use of fruits (whether apples or not) has occurred over the same years which have seen the remarkable increase in sugar consumption above referred to.

SUMMARY AND CONCLUSIONS

The increase in the incidence and death rate from diabetes in the United States, and in New York City in particular, has been more rapid than that of any other disease for which we have records in the last fifty years.

22. Riesman, D.: Quoted by Forsheimer, 1914, p. 718.

This increase, while it has affected all ages to some degree, has been most marked among women at all ages and among both men and women over 35 years of age in particular.

There are wide variations in the susceptibility to diabetes, or at least in their ability to survive when it develops in them, among persons of different races, those of Semitic stock showing consistently the highest death rates and those of the Negro race in the United States the lowest.

It is not at all clear that these marked differences in the death rates from diabetes in the people of various races are of fundamental biologic significance, since many elements of occupation, economic status, dietetic habits, etc., may be found sufficient to explain the range of experience with what may fairly be considered a disease of a fatigued function in the great majority of cases.

Although the relative rarity of diabetes among rural workers and those engaged in hard manual labor or trades would appear significant, the lack of a thoroughly satisfactory basis for calculating death rates by occupational groups in this country deprives the contrasting picture, of high rates among desk workers and others engaged chiefly in mental rather than physical processes for their living, of much of its force.

Seasonal variations in death rates, calculated on a monthly basis, are marked and apparently significant. Whether temperature and other accompanying weather conditions are responsible, or the similar seasonal incidence of infections, usually accompanied by fever and interference with nutrition and deteriorated bodily resistance, cannot be stated on the basis of present information.

Geographical distribution of the disease as measured by death rates in the United States appears to be explicable on the basis of differences in the age grouping, race, economic status, and occupation of the people, high rates being found where there is a high proportion of the population in the later decades of life, after 45, where there are many Jews and where per capita wealth is high. Where life expectancy is high there is a lower diabetes death rate than in states where life expectancy is low, but this is probably due to the fact that the low expectancy states are those with a high proportion of Negroes in the population.

The changes in food habits in the United States have probably contributed to the increase of diabetes, the higher carbohydrate element and greater abundance or superalimentation being believed to be a cause of overfatiguing the function of sugar tolerance.

It is considered of much importance that educational measures be instituted to inform the public through medical and public health channels of the seriousness of the situation, and of the necessity of adjustment of food intake to exercise and vice versa.

Moderation in the use of food and sufficient exercise with the entire body to justify the food absorbed, are important rules of hygiene for other reasons besides that of the relationship between obesity and diabetes, but if there were no other excuse for bringing this ancient teaching to people's attention, the greatly increased frequency of diabetes as a cause of sickness and death would alone seem to justify physicians and all those dealing with health and its protection in initiating and pushing vigorously a campagin of information in this subject.

ABSTRACT OF DISCUSSION

Dr. Louis I. Dublin, New York: Dr. Emerson is to be commended not only for bringing together for us these very interesting facts in regard to diabetes, but especially for his effort in utilizing a method which has rarely been used in the study of any of the degenerative diseases. As he pointed out, the method of the epidemiologist and the vital statistician has been used in the study of the communicable diseases, in tracing the causes and the interrelations of disease but rarely in such diseases as diabetes, nephritis, heart disease and the others where obviously we are not concerned with an infective organism. The value of this new method is not only in giving us a glimpse into the natural history of the particular disease, but also in permitting us to make comparisons and in finding those diseases which are of a similar character. You will remember that he showed that diabetes had a heavy incidence among females, a heavier incidence among whites than among the colored, that it had a very definite racial incidence, particularly among the Jews and Irish. If you begin to look for other diseases that show similar characteristics you soon find them. Take a disease like exophthalmic goiter, for example, it has these very characteristics, heavier incidence among females than males, heavier among whites than among colored and a special incidence among certain stocks. Addison's disease is another. I might list two or three others which show exactly these same relations. It is clear that we are concerned here with a group of diseases that have a similar origin. We are concerned in diabetes, exophthalmic goiter and Addison's disease with disorders of endocrine function, and no wonder we get the same kind of a picture when we plot the incidence of these diseases in this way.

It is true that diabetes has increased rapidly in recent years. It has increased more rapidly, however, in certain areas than in others. It has increased in those areas where people who are more inclined to diabetes live. The enormous increase in the city of New York is obviously due to the large increase in the number of Jews in that community, also in the number of Irish. I may say, also, that there are a number of phenomena in this disease which future research will have to clear up. Here and there in the study of the figures for localized areas we encounter conditions which are very difficult to explain on any theory. While it is true that very generally the colored race has a low incidence compared to the white race, there are states in the South in which the condition is reversed and that is especially true of the urban populations. In studying the figures for insured lives in the Metropolitan Insurance Company, we are struck with the fact that in certain southern communities in which the number of negroes is very large, the rates are higher for the colored than for the whites, but just why, I do not know.

Finally, I would call attention to the fact that during the last year and a half, in fact, since the beginning of the very general use of insulin, the marked increase in the diabetes death rate seems to have come to a stop. I am the last one to draw conclusions from a solitary and isolated fact like this covering a very short period. I would call attention, however, to the fact that during the last twenty years, the death rate from diabetes has mounted as no other

condition. It has jumped a number of points a year. Certainly when this disease suddenly stops rising and begins to fall month by month and falls more rapidly with advancing time, it is suggestive that the increased use of insulin may be producing this result. It looks like a remarkable illustration of the efficiency of the new therapeutic agent.

Dr. Eugene L. Fisk, New York: Dr. Emerson has shown us a wonderful exposition of the fact that diabetes is something more than a cloud as big as a man's hand on the civilized horizon. While we are urging immunization against typhoid and vaccination against smallpox and measures of that sort we might well urge with more emphasis not only the periodic examination of the urine, but blood sugar tests, especially in middle aged people who tend to overweight; that is, the type of person who has been hinted at as the one most likely to have this trouble. I can give you a single instance of a tragic result from not following such custom—a sign of warning not to rely too much on the routine examination of the urine alone. A middle aged man, about 30 pounds overweight, showed a trace of albumin and a few hyaline casts in his urine, but no sugar. He was warned about these conditions, and advised to have the urine examined periodically; in addition, he was urged to have blood sugar examinations made, a warning he ignored. He got no encouragement from his physician to have that done as he had no sugar in the urine. That man died within eighteen months of diabetes. Now one death of that kind in a group of that sort is one death too many and I think health officers and others could with just as much reason urge functional tests of kidneys and blood tests to aid in checking inroads of disease like this as to advise vaccination, the Schick test and other measures commonly employed to combat communicable diseases.

Dr. Isaac I. Lemann, New Orleans: While there is less diabetes among the negroes than among whites, it is probable that the same cause that is operating to increase the diabetes among the whites is operating to exactly the same extent to increase diabetes among the negroes. I have compiled statistics from the Charity Hospital of New Orleans during two decades, from 1900 to 1910 and from 1910 to 1920. While the negroes contributed in this period somewhat less than one-half of the total admissions of the hospital, they contributed something less than their share of diabetes. Their share of diabetes was about one-third less than would have been expected as based on their proportion of admissions. That was true of both periods. When we compared the total incidence of diabetes in the two periods we found that it had gone up very markedly. We found, also, that the rate at which it had increased was exactly the same in the negroes as in the whites. So that we draw the conclusion that the same conditions were operating to increase it in the two races. It is worth while to note in this connection that there is nothing in the statistics to bear out the suggestion of Warthin that syphilis plays a rôle in the production of diabetes, for the negroes in these groups contributed a very much larger share of the syphilitic diseases, as everybody knows, but exhibited a less share of diabetes.

Dr. Haven Emerson, New York: In considering the reduction in the diabetes death rate during 1923 and the first quarter of 1924 in New York, it is worth while to bear in mind that similar and quite as extensive drops in the rate have occurred as shown in the chart already presented, particularly in 1890 and during and after the influenza epidemic and food restriction periods of 1917 to 1919. Although it is possible that insulin is the main factor in the reduction of diabetes death rates in the last eighteen months, in this city and elsewhere in the United States, we cannot be sure of this until the reduction has continued for a considerably longer period. With regard to the effect of overliberal diets in causing diabetes, I must call your attention to the fact that while in the United States 150 pounds of meat is used per capita per annum, the people of Australia use 250 pounds per capita and the discrepancy between these two is made up in the United States chiefly by increased per

capita consumption of sugar, cereals, milk, vegetables and fruits. It would appear to me that evidence presented in my report supports the contention of Allen to the effect that much diabetes, among the wealthy in particular, is due to a fatigue of the function of carbohydrate tolerance by an attempt to assimilate a diet which overstrains this function. Apparently, among the reasons for the low rate among negroes is the fact that their occupations involve chiefly the use of the heavy muscles of the trunk and legs and arms, whereas the occupations of those among whom diabetes is most common involve the least physical effort.

THE ASSOCIATION OF HYPERTENSION WITH SUPRARENAL TUMORS *

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That tumors of the suprarenal gland may be associated with hypertension was first pointed out by Edmund Neusser.[1] He observed two patients in whom the condition ran the typical clinical course of nephritis with hypertension, but at necropsy the kidneys and arteries were found not affected, the pathologic finding in each instance being a neoplasm of the suprarenal gland, described as a carcinoma by Neusser. These observations attracted little attention till Vaquez,[2] influenced by Josué's discovery of the vascular lesions produced by epinephrin, formulated the doctrine that arterial hypertension is due to hyperepinephrinemia. It was shown that diffuse hyperplasia and circumscribed adenoma formation in the suprarenal cortex are exceedingly common in persons suffering from hypertension, whether it is nephritic or what is now termed "essential" hypertension. Thus, Aubertin and Ambard [3] found that out of eight cases of hypertension four showed diffuse cortical hyperplasia and three others adenomas of the suprarenal cortex; in only one instance was the gland normal. Philpot [4] found that the weight of the suprarenals is much greater in sufferers from chronic nephritis than in comparable material of the same age group without nephritis. In a series of thirty cases of hypertension one of us found cortical adenomas present in five instances, while in fifty successive necropsies in which no hypertension had been present, adenomas were found in only one case (and even in this solitary instance the kidneys were granular).

It is thus seen that there is considerable anatomic evidence that hyperplasia of the suprarenal glands is a frequent concomitant of arterial hypertension. Unfortunately, the functional interpretation of these changes in the suprarenals presents a very difficult problem. In most instances the hyperplasia noted has involved the cortex, though a few authors (Wiesel,[5] Parkinson,[6] etc.) have observed enlargement of the

* From the Medical Division of the Montefiore Hospital.
* Read before the American Society for Clinical Investigation, May 5, 1924.

1. Neusser: Nothnagel's Spezielle Pathologie und Therapie, Vienna, **18**:71, 1898.
2. Vaquez: Tr. Cong. franç. de méd., 1904, p. 338.
3. Aubertin and Ambard: Bull. ét mém. Soc. méd. d. hôp. de Paris **21**:175, 1904.
4. Philpot: Quart. J. Med. **3**:34, 1909.
5. Wiesel: Verhandl. d. Kongress f. inn. Med. 1907, p. 221.
6. Parkinson: Tr. Path. Soc. London, **58**:187, 1907.

medulla, which is rather what one would expect if the hypertension is to be attributed solely to a hyperepinephrinemia. Despite the initial, seemingly successful, experiments of Schur and Wiesel,[7] using a technic that has not withstood criticism, an increase in the epinephrin content of the blood has never been proved to exist in patients suffering from hypertension. In fact, even the presence of epinephrin in the general circulation has not been demonstrated unequivocally, though exceedingly delicate biologic reactions have been applied. Schmorl's [8] analyses of suprarenal glands from hypertensive subjects did not show them to contain more epinephrin than do the suprarenals of persons with a normal arterial tension.

In view of the well known action of epinephrin in mobilizing hepatic glycogen, it might well be supposed that one of the manifestations of an increased epinephrin content of the blood would be hyperglycemia. In accordance with this, Neubauer [9] was the first investigator to show that the blood sugar is usually increased in hypertensive subjects, and this has been confirmed by most subsequent investigators, particularly in vascular (essential) hypertension.

The table summarizes our findings in eleven patients presenting hypertension in whom blood sugar determinations were made, and who subsequently came to necropsy.

Blood Sugar Findings in Eleven Patints with Hypertension

Number	Blood Pressure	Blood Sugar (Mg. per 100 C.c.)	Pancreatic Arterioles
1	204/100	150	Markedly thickened
2	220/100	156	Normal
3	180/110	110	Normal
4	180/135	132	Slightly thickened
5	208/132	122	Normal
6	210/94	152*	Markedly thickened
7	220/140	95	Markedly thickened
8	170/100	142*	Slightly thickened
9	240/150	134	Moderately thickened
10	225/100	130	Thickened
11	210/118	151	Slightly thickened

* Glycosuria.

The foregoing determinations of the blood sugar were made by the method of Folin and Wu, with which the normal values range below 120 mg. per hundred cubic centimeters. It is seen that in eight of the eleven cases the blood sugar is definitely above the normal, while in one of the remaining three instances it is at the upper limit of the normal. In two of the patients the blood sugar exceeded the renal threshold with resulting glycosuria. But in no case was the blood sugar level as high as is usually seen in true (pancreatic) diabetic

7. Schur and Wiesel: Wien. klin. Wchnschr. **20**:699, 1907.
8. Ingier and Schmorl: Deutsch. Arch. f. klin. Med. **104**:262, 1911.
9. Neubauer: Biochem. Ztschr. **25**:284, 1910.

patients on an unrestricted diet, though Hitzenberger and Richter-Quittner [10] of Falta's clinic have reported such high values in patients with hypertension. Schwab,[11] the results of whose determinations agree with ours, explains the high readings of these authors by the technic that they employed. A study of the table reveals no close parallelism between the height of the glycemia and the blood pressure.

Pancreatic arteriosclerosis of more or less marked severity was present in eight of the eleven cases listed in the table. Here again there seems to be no close correlation between the degree of the hyperglycemia and the severity of the vascular changes. In fact, the lowest blood sugar reading recorded was in a patient with extremely severe sclerosis of the pancreatic arterioles. It is common to see at necropsy severe sclerosis of the pancreatic vessels where no hyperglycemia existed during life, but it should be borne in mind that the arteriosclerosis of the larger arteries as seen macroscopically is very different in its consequences for the parenchyma of the organ than the arteriosclerosis of the finer arterial radicals to which we refer in the table. The fact that the the hyperglycemia does not attain any great height, despite the long continued lack of dietary control, seems also to differentiate it from the ordinary pancreatic hyperglycemia. Nevertheless, in view of the comparative frequency of pancreatic arteriosclerosis in hypertonic subjects, it does not seem justifiable without further evidence to attribute the increased blood sugar to a heightened secretion of epinephrin, though this is certainly a strong possibility.

It is thus seen that neither experimental evidence nor chemical and pharmacologic study of the blood lend much support to the attractive hypothesis ("beautiful dream," as the late T. C. Janeway [12] called it) of an excessive epinephrin content of the blood in hypertension. It is our aim in the present communication to point out that in certain, though rare, instances neoplasms of the suprarenal gland produce chronic arterial hypertension.

TUMORS DERIVED FROM THE SUPRARENAL MEDULLA

In accordance with the development of the medulla from the formative cells of the sympathetic ganglions, three varieties of tumors have been found:

1. Sympathoblastomas, made up of immature sympathoblasts.

2. Ganglioneuromas, consisting of relatively mature sympathetic ganglion cells, in which differentiation has gone further than in the tumors of Group 1.

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10. Hitzenberger, K., and Richter-Quittner: Wien. Arch. f. inn. Med. **2**:2, 1921.
11. Schwab: Virchows Arch. f. path. Anat. **242**:1, 1923.
12. Janeway: Am. J. M. Sc. **145**:638, 1913.

3. Paragangliomas (pheochromocytomas, L. Pick), made up of apparently mature chromaffin cells.

Only in connection with the rare paragangliomas (chromaffin tumors) has hypertension been reported. In the literature we have found the following five cases of paragangliomas with adequate blood pressure observations or the anatomical equivalent of hypertension (cardiac hypertrophy in the absence of all renal, arteriolar, valvular or other lesions which might cause hypertrophy).

1. Orth [13] found at necropsy a case in which the intra vitam diagnosis was chronic nephritis (blood pressure, 220 systolic, 140 diastolic). At the necropsy the kidneys and arterioles were normal but there was a paraganglioma of the suprarenal gland in which Orth was able to demonstrate, both microchemically and by biologic reactions, the presence of large amounts of epinephrin.

2. In a patient, aged 2½ years, with paraganglioma of the suprarenal, Wiesel [14] found very advanced arteriosclerosis with medial changes similar to those occurring after the experimental injection of epinephrin.

3. Bergstrand [15] found a suprarenal paraganglioma in a patient presenting large cardiac hypertrophy (weight of heart 500 gm.) with no renal, arterial or valvular lesions.

4. Labbé, Tinel and Doumer [16] observed a woman, aged 28, whose blood pressure varied greatly, though it was nearly always very high. During some of the paroxysms of hypertension the blood pressure was as high as 280 systolic and 190 diastolic. At times it was as low as 120 systolic, and 80 diastolic. Tremendous fluctuations occurred in the course of the same day. During the paroxysms of extreme hypertension, the patient presented signs of peripheral vasoconstriction, such as pallor and coldness of the extremities. There were evidences of sympathotonia: tachycardia, mydriasis, etc. At times the urea nitrogen of the blood was very high, but later this became normal. The symptoms lasted for several months, till they finally terminated in acute pulmonary edema. The sole cause for the hypertension revealed by the necropsy was a paraganglioma of the suprarenal. The only lesions found in the kidneys were some interstitial hemorrhages and a number of foci of coagulation necrosis of the tubular epithelium, which the authors considered as due to the ischemia resulting from intense vasoconstriction. The heart weighed but 340 gm.

5. In contradistinction to these observations, Thomas [17] examined a case of paraganglioma of the suprarenal in which there was no evi-

13. Orth: Sitzungb. d. k.- Preussichen Akad. d. Wissensch. **11**:34, 1914.
14. Wiesel: Der heutige Stand der Lehre von der Arteriosclerose, Vienna, 1909.
15. Bergstrand: Hygeia, Stockholm **82**:321, 1909.
16. Labbé, M.; Tinel, J., and Doumer: Bull. et mém. Soc. méd. d. hôp. de Paris **46**:982 (June) 1922.
17. Thomas: Frankfurt. Ztschr. f. Path. **16**:376, 1915.

dence of hypertension. However, the patient, aged 80 years, was seen only terminally. It is quite possible that senile cachexia prevented the development of cardiac hypertrophy and hypertension, as it occasionally does in chronic nephritis.

There are numerous cases of ganglioneuroma and a few of sympathoblastoma of the suprarenal recorded in the literature, but none show any evidence of hypertension. Nor does hypertension occur when tumor metastases are present in the suprarenals. Evidently, then, only the paragangliomas among the tumors of the suprarenal medulla may be accompanied by hypertension, as in four of the five instances recorded in the foregoing.

TUMORS DERIVED FROM THE SUPRARENAL CORTEX

We have noted in the foregoing the frequent finding of diffuse and circumscribed (adenomatous) hyperplasia of the suprarenal cortex in cases of hypertension. Also before mentioned were the difficulties encountered in interpreting the statistically evident correlation between the cortical hyperplasia and the increased blood pressure. Does the diffuse or nodular cortical enlargement bear a causal relationship to the hypertension, is it merely a reaction of the cortical cells to products of renal retention (the work of the Aschoff school has shown that the suprarenal cortex has an important detoxifying function), or is it the result of the arteriosclerosis found in the vast majority of cases of hypertension? Whichever of these explanations is correct for the ordinary cortical hyperplasias, there are in the literature the following few instances in which there seems little reason to doubt the causal connection of a tumor of the suprarenal cortex and the hypertension in the particular case:

1. Bland-Sutton [18] reports a case of tumor of the suprarenal cortex, in which there was enormous cardiac hypertrophy for which he could find no other cause.

2. Bullock and Sequeira [19] observed a child, aged 11 years, who was fully matured sexually and had hypertension; at necropsy a tumor of the suprarenal gland was found, with the morphology of the cortex.

3 and 4. The two cases of Neusser,[1] before mentioned, belong to this group.

5 and 6. Of very great interest are two cases observed by Volhard,[20] in which the clinical picture was that of diffuse nephritis with hypertension and albuminuria. In each instance after operative removal of a hypernephroma the hypertension disappeared.

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18. Bland-Sutton, J.: Brit. M. J. **2**:593, 1918.
19. Bullock and Sequeira: Tr. Path. Soc. London, **56**:189, 1905.
20. Volhard: Mohr and Staehelin's Handbuch der inneren Medizin, Berlin, **3**:1291, 1918.

7. Mackintosh [21] observed a boy, aged 14 years, presenting obesity, hirsuties of forehead, eyebrows, chin, axilla and pubis. Striae atrophicae were present on the abdomen. Glycosuria was found. The blood pressure was 240 systolic, 170 diastolic. The left lower ribs bulged and the author considered the case one of suprarenal hyperplasia. (Note the minute resemblance to our Case 2 reported further.)

8. Hoag [22] communicated the following exceedingly interesting case, with a necropsy report by Warthin: A girl, aged 4 years, had precocious sexual development. The blood pressure ranged from 160 to 145 systolic, and from 100 to 90 diastolic, a tremendous hypertension for a child of that age. Necropsy revealed a hypernephroma and arteriosclerosis of the pial vessels.

9. Mathias [23] reports the case of a girl, who, at the age of 3 years, was sexually mature and had a well marked beard. She died at the age of 18, the necropsy revealing a hypernephroma, as well as marked hypertrophy of the left ventricle. No blood pressure readings are recorded, but the necropsy protocol reveals no cause for the cardiac hypertrophy in the kidneys, arterioles or valves of the heart.

We have recently had the opportunity of studying the following case, in which the pathogenetic rôle of the suprarenal tumor seems unequivocal.

CASE 1.—M. F., a man, aged 24, was admitted Jan. 11, 1923, complaining of dyspnea on exertion and palpitation, both symptoms being only of three months duration.

The family history was irrelevant. The patient denied having any previous illness.

About three months prior to his admission to the hospital, the patient began to experience palpitation and dyspnea on exertion, which grew progressively worse. He also complained of precordial pain, without well defined radiation. Shortly before admission the patient began to have a dry cough and noted a pain in the right axilla.

The patient's replies indicated mental deficiency.

Physical Examination.—A well developed and well nourished young man, breathing rapidly and with obvious effort was seen. He was not cyanotic. The prominent supraorbital ridges, heavy jaw, large hands and feet, and thick eyebrows meeting in the midline gave the patient an acromegalic appearance.

The head and neck organs presented no significant deviations from the normal.

Lungs.—Slight impairment at right base posteriorly. A few râles were heard at both bases.

Heart.—The somewhat diffuse apex beat was felt in the sixth interspace, outside the nipple line. Percussion revealed that the heart was enlarged to either side, the left border being 14 cm. from the midline in the sixth interspace and the right border 5 cm. from the midline in the fourth interspace.

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21. Mackintosh, Ashley: Quart. J. Med. **14**: "Proceedings," following p. 108, 1920.

22. Hoag, Lynne: Malignant Hypernephroma in Children, Am. J. Dis. Child. **25**:441 (June) 1923.

23. Mathias: Virchows Arch. f. path. Anat. **236**:446, 1922.

The sounds at the apex were fairly loud; a presystolic gallop rhythm was heard here. The second sound was accentuated at the aortic area. A short systolic murmur was audible at the base.

Pulse.—The radial artery felt thickened. The tension was high, but alternate beats felt weaker. The blood pressure was 200 systolic, and 150 diastolic. The presence of the pulsus alternans was proved by the manometric readings, and by polygraphic tracings.

Examination of the abdomen, extremities, genitalia, lymph nodes, and reflexes revealed no abnormalities.

The blood examination disclosed a slight secondary anema.

Urine.—Spontaneous concentration was 1.025. Albumin was usually present, sometimes in considerable quantities. On most examinations casts were absent: occasionally some hyaline and granular casts were found. White blood cells were usually present, but never any erythrocytes.

Blood Chemistry.—The following were the results expressed in milligrams per hundred cubic centimeters.

Date	1/13	1/20	2/10	2/21	3/2	3/21*
Urea nitrogen	22.4	14.0	18.2	24.9	11.0	11.9
Nonprotein nitrogen	50.2	34.1	30.7	....	....	....
Uric acid	2.5	2.7	2.1	6.0	2.1	....
Creatinin	1.2	1.3	0.9	....	....	....
Sugar	....	....	....	156.0	....	106.0
Cholesterol	....	....	....	....	206.0	....

* Six days before death.

Phenolphthalein elimination 50 per cent. (after intramuscular injection), on two occasions.

Fundus Oculi.—Right eye. The nerve head was red, its margins indistinct. The veins were engorged, the arteries extremely narrow and in places lost. There was perivasculitis. The left eye was the same as the right eye but there were numerous fine spots of degeneration between the nerve head and macula, and a few spots of fibrinous exudate above and to the dorsal side of the nerve head. Diagnosis: Albuminuric retinitis, arteriosclerosis (?).

Blood Wassermann was negative.

Electrocardiogram.—T was inverted in Leads I and II and small in Lead III. R showed distinct slurring.

The sella turcica was rather large and shallow in the stereoroentgenogram.

During the patient's stay in the Mt. Sinai and Montefiore Hospitals he continued to suffer from dyspnea, palpitation and other evidences of myocardial insufficiency. The blood pressure remained around 220 systolic, 160 diastolic, and the alternation of the pulse persisted.

March 7, the patient showed signs and symptoms of bronchopneumonia. His condition gradually grew worse, he became delirious and died March 27. The total time that elapsed between the onset of symptoms and death was less than six months.

In view of the hypertension in the absence of any evidence of renal insufficiency, or even of renal involvement other than chronic passive congestion, a diagnosis was made of vascular (essential) hypertension with secondary myocardial insufficiency.

Necropsy.—The head and neck organs were negative (the retina was not examined).

Heart.—Enormously hypertrophied and dilated, and weighed 880 gm. Hypertrophy was most marked in the left ventricle, the walls of which measured 22 mm. in thickness. The heart muscle was slightly fatty. Aside from slight atherosclerotic patches on the mitral and aortic cusps, the valves were normal. The coronary arteries showed a few fatty flecks but everywhere were smooth

and patent. The aorta was normal, only a few small fatty areas around the mouths of the branches being seen. The larger vessels throughout the body appeared normal, though the vessels forming the circle of Willis felt thicker than usual.

Lungs.—Bilateral bronchopneumonia and edema.

The kidneys together weighed 320 gm. The capsule stripped with some difficulty, revealing a slightly irregular, reddish-brown surface on which there were some yellowish flecks. The markings were somewhat blurred. The larger renal vessels were slightly thickened. In the cortex of the right kidney was an organized infarct.

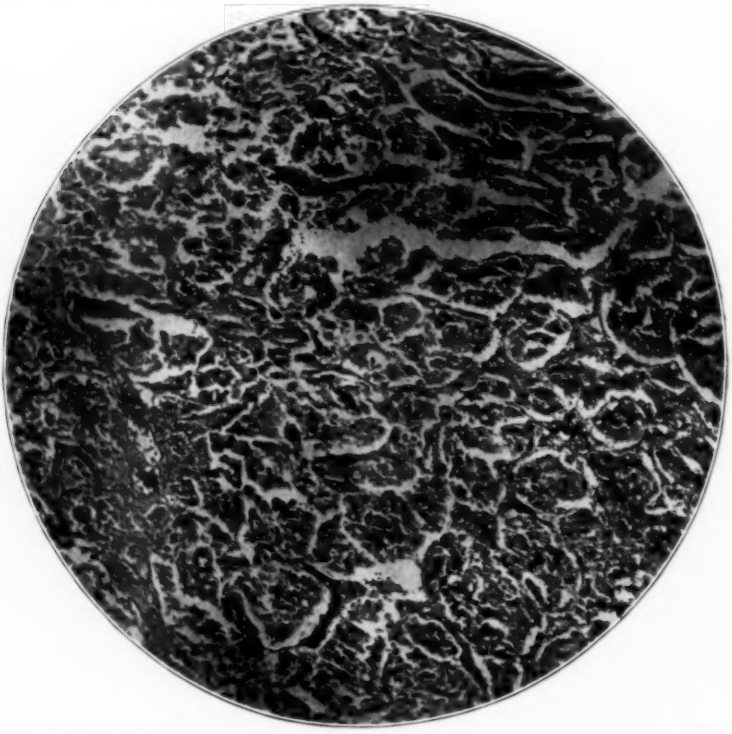

Fig. 1.—Photomicrograph of section of tumor of the left suprarenal gland (Case 1). Cells arranged in alveoli; septums consist of capillaries filled with blood (low power).

Microscopically, congestion was immediately evident, many of the glomerular loops as well as the intertubular capillaries being distended with blood. The finest arterioles (vasa afferentia to the glomeruli) showed no evidence of arteriosclerosis, either in the hematoxylin-eosin, Mallory or elastin (Weigert) preparations. A few of the larger arterioles (arcuate and interlobular vessels) showed distinct intimal thickening. The medial musculature of these arterioles appeared somewhat thicker than usual and in places the muscle cells stained poorly. Nearly all the glomeruli appeared normal aside from congestion. There was neither epithelial nor endothelial proliferation,

nor was there evidence of exudation into the glomerular capsules or tufts, the loops of the latter containing numerous red cells. There were a few minute foci of glomerular fibrosis, but their number was very small. Around one glomerulus was a moderate pericapsular fibrosis. Some of the tubules contained pink staining casts. A few of the convoluted tubules were dilated and lined by low epithelium. There was slight epithelial desquamation.

Suprarenal Glands.—The right weighed 25 gm. It measured 6 by 4 by 2.5 cm. Nearly all of the gland was replaced by a large tumor mass involving both the cortex and medulla; only a small portion of normal tissue containing

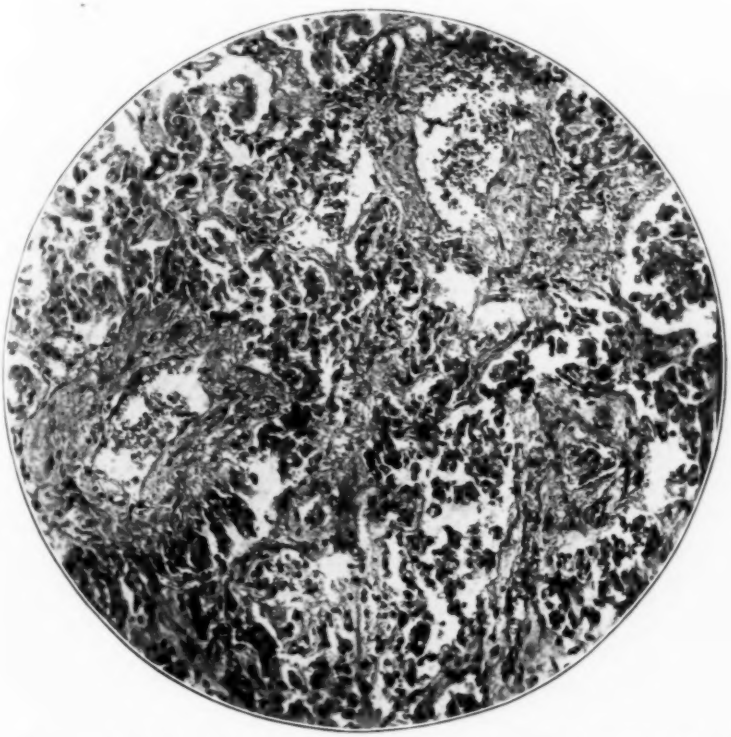

Fig. 2.—Section from periphery of tumor of left suprarenal. Shows a typical proliferation of cells (high power).

both cortex and medulla was seen at one end. The tumor was soft, somewhat elastic and grayish in color, and contained yellow necrotic portions. The left suprarenal gland weighed 10 gm., and on section was seen to contain ten small cortical adenomas. Aside from the adenomas the cortex was hyperplastic.

Sections through the left suprarenal showed the adenomas to be of the usual structure, made up of cortical cells rich in lipoids and arranged in rather irregular fascicular formations. Sections of the large tumor of the right suprarenal revealed a different appearance. In places the resemblance to the cells and arrangement of the cortex was readily seen, elsewhere more atypical proliferation had occurred. The cells had either vesicular or deeply staining

nuclei and the cytoplasm of most cells stained uniformly pink, giving no evidence of high lipoid content. The cells had an alveolar arrangement, but the septums in places contained little connective tissue, being composed almost entirely of well filled blood capillaries (Figs. 1 and 2). There were extensive areas of necrosis, and here and there were the remains of hemorrhages. There were scattered phagocytic cells loaded with hemosiderin. It seems reasonable to believe that this larger mass originated from a cortical adenoma (struma suprarenalis of Virchow), which started to proliferate more vigorously and now gives a histologic picture resembling hypernephroma. The histogenesis was apparently quite analogous to the development of malignant growths from ordinary adenomas of the thyroid, which Marine believes to be the almost invariable starting point of thyroid carcinomas. No accessory suprarenal tissue was found along the spermatic cord or elsewhere.

The other organs presented no significant pathologic changes. The smaller arterioles in the various viscera were not thickened, except for slight hyalinization in some of the arterioles of the spleen.

The essential intravitam and necropsy findings may be summarized as follows: A youthful patient presented a blood pressure of 220 mm. of mercury [24] systolic, 160 diastolic, with great cardiac hypertrophy. There was no evidence of kidney disease. Renal function was totally intact, the urea nitrogen being 11.9 mg. per hundred cubic centimeters of blood six days before death. At necropsy, tremendous cardiac hypertrophy (weight of heart 880 gm.) was found. No valvular lesion was present. The renal lesions were slight, focal and not diffuse, and evidently secondary to the slight arteriolar lesions. It is to be emphasized that the latter were found in only a very few vessels, the large majority being normal. Almost all of the glomeruli were intact, and it is inconceivable that the hypertension could be attributed to the few fibrotic foci. The usual explanations of cardiac hypertropny, valvular, diffuse renal or arteriolar lesions, fail us in this instance. But there was a tumor of the suprarenal cortex, and in the light of the findings of previous investigators detailed in the foregoing, there seems no reason to doubt a causal connection between the hypertension and the tumor of the suprarenal gland.

Parenthetically, we may call attention to the "albuminuric" retinitis, which the patient presented in the absence of renal insufficiency or hypercholesterinemia. The arteries of the fundus, as is usual in this condition, were very narrow in places lost. The occurrence of these changes in the eye-grounds in this case confirms the view of Volhard [25] that albuminuric retinitis is due to ischemia produced by a narrowing of the retinal arteries, and is not necessarily the consequence of retention of urinary constituents.

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24. The exceedingly high diastolic pressure furnishes a measure of how great the peripheral resistance must have been. (See also the cases of Labbé, Tinel and Doumer and of Mackintosh.)

25. Volhard: Verhandl. d. deutsch. Gesellsch. f. inn. Med. **33**:422, 1921.

We add the following juvenile case, although unfortunately no necropsy was obtained. But the clinical picture was so characteristic of suprarenal hyperplasia as to leave little doubt of the diagnosis.

CASE 2.—S. G., a girl, aged 12, was admitted to the Montefiore Hospital complaining of weakness and adiposity. Her family history contained no items

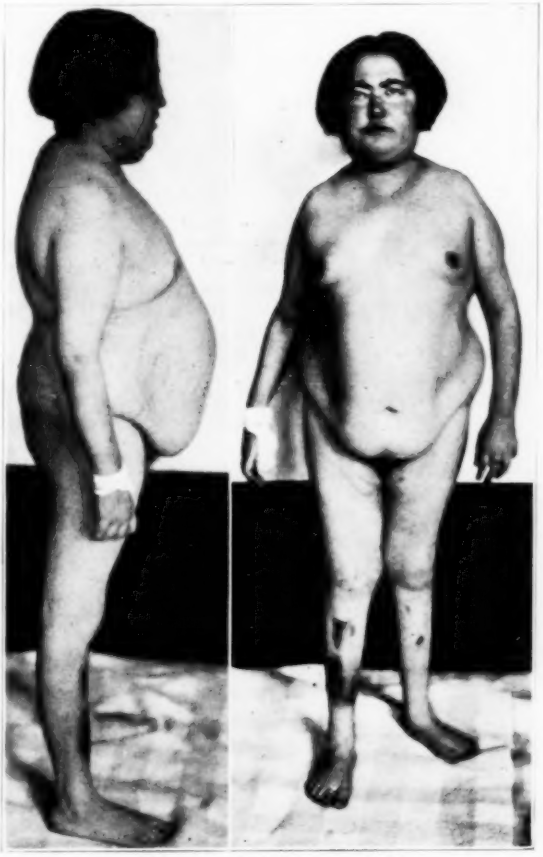

Fig. 3.—Side and front view of Case 2, a girl, aged 12 years, showing pubertas precox, obesity, hirsuties of the chin, cheeks and eyebrows; striae atrophicae of abdominal wall, and the physique of an adult woman.

of interest. Between the ages of 9 months and 2 years the patient suffered from fainting spells. Strabismus was present since infancy. The patient underwent an operation for double cataract at the age of 5. About this time she had scarlet fever, complicated by pyelitis.

The present illness dated back seven years, when the patient was aged about 5½ years. She suddenly began to gain in weight and became disproportionately

adipose, gaining about 75 pounds (34 kg.) in one year. She was seen by many physicians and treated symptomatically with various glandular preparations. About a year ago the parents noticed a change of skin coloration. The patient developed a tendency to fall asleep. A routine urine examination revealed 4 per cent. of sugar. Polyuria and nocturia developed about this time. At the age of 11 hair began to grow on the face, axilla and pubis. The patient had never menstruated.

Physical Examination.—An undersized child, appearing many years older than her actual age, was seen (Fig. 3). She was exceedingly obese and had a very red, plethoric facies. There was a well marked growth of hair on the chin and lower cheeks. The pubic and axillary hair were well developed. On the abdomen were pigmented striae.

Eyes.—Bilateral aphakia. Satisfactory examination of the fundus was impossible. The other head and neck organs were negative.

Heart.—Enlarged to the left. The sounds were of good quality. The second sound was accentuated over the aortic area. There were no murmurs.

The blood pressure was 190 systolic, 130 diastolic.

Skin.—There were abscesses on the back and neck, and a mycotic infection of the nails. There was no edema whatever. There were ulcers on the legs.

Urine.—Spontaneous concentration to 1.022. Sugar was present, but no acetone bodies. There was a heavy cloud of albumin. Microscopic examination revealed neither casts nor cellular elements. Phenolsulphonephthalein elimination, 45 per cent. (after intravenous injection).

Blood Chemistry.—Urea nitrogen, 11 mg., uric acid, 5 mg., sugar 260 mg. per hundred cubic centimeters.

Blood Count.—Erythrocytes, 4,500,000; leukocytes, 11,000, of which 78 per cent. were polymorphonuclear, 16 per cent. lymphocytes, 5 per cent. monocytes, and 1 per cent. esinophils. Hemoglobin, 90 per cent. (Sahli).

Basal Metabolism.—Plus 1, minus 3 per cent.

Roentgenography revealed no changes in the sella turcica.

The patient was placed on an antidiabetic diet and digitalized. The urine rapidly became normal, the sugar and albumin disappearing completely. At one time signs and symptoms of bronchopneumonia appeared, but these cleared up. The abscesses of the neck and back healed and her parents insisted on removing the child from the hospital. We then lost sight of her, but recently obtained information that she had died three weeks after leaving the hospital.

SUMMARY

At the age of 5 years, a girl suddenly started to gain weight rapidly, taking on 75 pounds (34 kg.) in a year. Glycosuria developed but the patient remained very fat. In addition to this she showed very markedly precocious development of the secondary sexual characteristics, though she did not menstruate. Also, a heterosexual growth of hair appeared on the cheeks and chin. In other words, she presented that combination of obesity and precocious sexual development which Parkes Weber has designated as "precocious obesity." The triad of sexual precocity (pubertas praecox), obesity and development of heterosexual virilism are practically pathognomonic of hyperplasia or tumor of the suprarenal cortex in young children, especially in girls, being differentiated from ovarian or pineal precocity by the heterosexual hair and from the adiposity of pituitary lesions (Froehlich's syndrome) by the sexual

precocity. The twelve cases of pineal tumor causing precocity collected by Boehm [26] were all in boys; they usually have the classical symptoms of brain tumor.

COMMENT

Of interest to us in the present connection is the hypertension in the absence of any evidence of nephritis, the albuminuria present at one period disappearing on digitalization. The patient was exceedingly plethoric, presenting the appearance seen in the essential hypertension of adults ("roten Hochdruck" of Volhard [27]), and quite a contrast to the pallor often seen in nephritic patients. In general, extensive arteriosclerosis is exceedingly rare in a child, aged 12 years; moreover, in this patient none of the palpable vessels felt sclerosed. Despite the unfortunate lack of anatomic confirmation, it seems justifiable to diagnose the presence of a hyperplasia or neoplasm of the suprarenal cortex in this case, and to attribute to this the otherwise inexplicable hypertension of a child, aged 12, not suffering from nephritis. Whether the diabetes was merely coincidental or whether it was of suprarenal origin we are not in a position to say.

From the two patients reported in the foregoing and the other confirmatory cases collated from the literature, it is seen that cases of hypertension occur in association with suprarenal tumors, particularly in youthful subjects. In Case 1 we were able to demonstrate anatomically that there were no considerable lesions of the kidneys or arterioles which could be held responsible for the hypertension. The two cases of Volhard, before mentioned, in which hypertension disappeared after the removal of a hypernephroma, seem to prove that in these cases the hypertension was due to the tumor.

The pathogenesis of the hypertension in cases of suprarenal tumor seems difficult of interpretation. We have seen, that of the tumors of the medulla, only those composed of mature chromaffin cells, the paragangliomas, are accompanied by hypertension (in four out of the five published cases), while the primary sympathoblastomas and ganglioneuromas, as well as all metastatic growths, are unaccompanied by hypertension. And while most tumors arising from the cortical cells are not associated with hypertension, we have cited and described the foregoing cases with exceedingly high blood pressure. That it is not the destruction or irritation of the normal suprarenal tissue that is the cause of the hypertension is proved by the cases of Addison's disease due to metastatic neoplasms. The simplest view would be to explain

26. Boehm, quoted by Collett, Arthur: Genito-Suprarenal Syndrome (Suprarenal Virilism) in a Girl One and a Half Years Old, with Successful Operation, Am. J. Dis. Child. **27**:219 (March) 1924.

27. Volhard: Verhandl. d. deutsch. Gesellsch. f. inn. Med. **35**:138, 1923.

the high blood pressure by an increased secretion of epinephrin, but this does not offer an immediate explanation of the increased arterial tension in cases of cortical tumor. In the case of Addison's disease, it is uncertain whether the low blood pressure and other symptoms are due to the destruction of the cortex or of the medulla; possibly the Addisonian symptom complex is to be attributed to a functional insufficiency of the whole gland. The symptoms of the cases of suprarenal tumor before described are, in several fundamental characteristics, diametrically opposed to those of Addison's disease. Thus the latter is characterized by subnormal blood pressure and hypoglycemia, while in the cases of suprarenal tumor there is more apt to be hypertension and hyperglycemia. It seems probable that the hypertension found in some cases of suprarenal tumor is due to an excess production of the same substance, the lack of which produces the symptoms of Addison's disease.

CONCLUSIONS

Clinically, the instances of suprarenal neoplasm listed present the picture termed, as a confession of ignorance of the pathogenetic factor, essential hypertension (R. Schmidt), or, having in mind the usual outcome, presclerosis (Huchard). It has long been realized that these names merely place in a common rubric pathogenetically and etiologically heterogeneous groups of cases, having in common hypertension in the absence of evidence of renal involvement. The great interest of the cases of hypertension associated with suprarenal tumors lies in the demontration that in certain instances (fifteen reported cases) of chronic non-nephritic hypertension the increased blood pressure is associated with an anatomically demonstrable lesion of the suprarenal gland, though the precise mechanism of the production of the hypertension remains unexplained. One small group of cases is thus removed from the great group of essential hypertension and may well be termed suprarenal hypertension.

SYPHILITIC AORTIC INSUFFICIENCY*

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Syphilis of the aortic orifice is now recognized as the most common cause of aortic insufficiency in adults. The disease is so frequently associated with syphilis of the aorta itself that, from a pathologic standpoint, one is not justified in considering the two conditions separately. Indeed, whether the aortic leaflets are ever primarily and exclusively attacked by syphilis, true syphilitic endocarditis, is still an open question. This, as well as several other interesting problems presented by the disease can best be studied by correlating clinical and pathologic observations on a large series of patients. Although the group of cases here discussed is not large, certain facts were observed which may serve as a basis for further study of what may be called syphilitic cardio-aortic disease.

This paper is based on the clinical and pathologic studies of twenty-five patients, who with but two exceptions, were under my observation at Cleveland City Hospital during the last three years. No selection of patients was made, as the group studied included all but four cases of syphilitic aortic insufficiency seen at the hospital during this time. Twenty-four of the patients were men and one was a woman. The youngest was aged 30, the oldest 64 years; the average age for the group was 40 years. Eighteen were between 30 and 45 inclusively, while three were between 60 and 64. Fourteen were white and eleven were colored. All had the signs of aortic insufficiency and, with one exception, all died of heart failure. The diagnosis was confirmed by postmortem examination in all cases included in this series. Physical exertion did not appear to be a determining factor in the heart failure, since at one extreme were laborers, at the other, a minister, a musician and a chauffeur; in a somewhat intermediate position a chiropractor.

SYMPTOMS AND CLINICAL COURSE

The abrupt onset and the progressive nature of the symptoms were, at least in this group of patients, characteristic features which appear in contrast to those seen in persons with aortic insufficiency from rheumatic infections. If, in addition, it is noted that our patients were usually well developed adults in the prime of life and with no previous cardiac history, the contrast is even more striking. Shortness of breath

* From the Medical Clinic of Western Reserve University at City Hospital.
* Read in abstract before the Association of American Physicians, Atlantic City, N. J., May 6, 1924.

and palpitation on exertion were the first symptoms observed by nearly every patient, and in response to the question, "When did you first notice undue shortness of breath?" they almost invariably specified a certain month or week. Prior to this time they had considered themselves well and able to work; in some instances at hard manual labor. The few who sought medical attention and were kept in bed at this stage were temporarily relieved; after getting up, however, they experienced the same incapacity for physical exertion as before.

The duration of symptoms before frank signs of heart failure appeared varied considerably. The longest period was three years in one case, the shortest two weeks, with an average of nine months. Twenty-four patients had varying grades of cardiac decompensation when first seen, and in spite of both symptomatic and antisyphilitic treatment, twenty ran a progressive downhill course to death. The four who were temporarily improved and left the hospital, were later readmitted one or more times and all died in less than a year. The longest hospital stay was seventy-eight days in one case, the shortest two days in three instances, with an average for the group of twenty-four days. Symptoms ordinarily attributed to syphilitic aortitis, i. e., substernal pain, nocturnal dyspnea, anginal attacks, etc., were noted in only one patient.

PHYSICAL SIGNS AND LABORATORY DATA

Only those physical findings which were more or less typical and common to the group as a whole will be considered here.

Excepting one case of tuberculous meningitis, the patients were well developed and well nourished. The excellent muscular development, particularly among some of the laborers, appeared quite consistent with their brief history of incapacity. In the white subjects, pallor of the face was the rule, but in no instance was this due to anemia, as shown by routine red blood counts and hemoglobin determination.

Most patients preferred the orthopneic position in bed. Respiratory distress closely paralleled the diminution in vital capacity from congestion at the lung bases, or more rarely, from a pleural effusion. A notable exception to this was seen in one case, J. R., who had violent dyspnea but good lung excursion, no signs of moisture at the bases, and a normal vital capacity. Cheyne-Stokes breathing was observed a few days before death in several instances. All cases, except two who were moribund when first examined, presented the characteristic vascular signs of aortic insufficiency. In approximately one-third of the patients one heard at the apex the typical presystolic Flint murmur, which in two instances was accompanied by a palpable thrill. The intensity of the thrill and the typical drum roll murmur in these two cases led two experienced observers to suspect mitral stenosis. At the

necropsy the mitral valves were normal in both cases. Without exception, every case in this series had both a systolic and a diastolic murmur, frequently more intense in the third or fourth interspace along the left sternal border than in the second interspace to the right of the sternum. The harshness, intensity, and duration of the systolic murmur in some cases, and as it happened in one instance, a palpable thrill over the base of the heart, might suggest a combined aortic stenosis and insufficiency.

It is interesting to note that arotic arch dilatation was suspected in several cases but not confirmed by necropsy. Not infrequently fairly typical signs of aortic widening were elicited, which were supported by roentgenologic examination. However, after finding aortas of normal caliber at the necropsy in several cases, it became apparent that caution was necessary in making a diagnosis of aneurysm in a case of frank aortic insufficiency, even in the presence of suggestive findings. The dynamic excursion of the aorta in this condition was long ago emphasized by Osler as one of the pitfalls in the diagnosis of aortic aneurysm.

Electrocardiograms were made in several cases, and although they were seldom strictly normal, there was no one abnormality which appeared characteristic.

Fever was present in all cases with pulmonary infarction but was unusual in the others. When it did occur it was seldom above 38 C. (100 F.). One patient, however, without pulmonary infarction had a persistent elevation in temperature (from 38 to 38.5 C.) (from 100 to 100.8 F.) for several weeks before death.

The high percentage of positive blood Wassermann reactions frequently found by past writers in cases of syphilitic aortitis was also found in this series. A positive blood reaction was obtained in all but one of the twenty cases examined. In this case the test was repeated several times and was consistently negative. This high percentage (95 per cent.) of positive reactions again emphasizes the significance of the test in the diagnosis of syphilis of the aorta.

NECROPSY FINDINGS

The necropsy material from this group of cases was interesting because of the uniformity with which certain findings appeared in every case (see the table).

ASSOCIATED SYPHILIS OF THE AORTA

Every patient showed syphilitic mesaortitis. In twenty, the lesion was demonstrable grossly as well as microscopically; in five, senile arteriosclerosis so obscured the gross picture that syphilitic mesaortitis could be proved only by histologic examination.

Clinical and Pathologic Findings in Twenty-Five Cases of Syphilitic Aortic Insufficiency

Patient	Sex*	Race	Age	Occupation	Duration of Life after Onset of Symptoms	Heart Weight, Gm.	Chief Defect at Aortic Orifice	Remarks
J. D.	♂	Black	45	Teamster	2 yr., 2 mo.	725	Sclerosed and retracted leaflets	
C. B.	♂	White	40	Pipemaker	3-4 years	...	Sclerosis and marked sagging of leaflets	
W. S.	♂	Black	39	Truck driver	2 months	700	Sclerosis and destruction of leaflets	
R. B.	♂	White	56	Electrician	2 months	650	Sclerosed and retracted leaflets	Right coronary artery occluded
C. D.	♂	White	28	?	5 weeks	600	Sclerosed leaflets, thickened throughout	
W. M.	♂	Black	35	Chauffeur	1½ years	800	Retracted sagging leaflets	
W. V. P.	♂	Black	58	Minister	6 months	470	Retraction of leaflets	
J. N.	♂	White	40	Laborer	2 weeks	440	Marked retraction of leaflets	Slight encroachment on orifice of right coronary
J. G.	♂	Black	40	Truck driver	3 weeks	740	Sclerosis and marked sagging of leaflets	
W. C.	♂	Black	39	Janitor	4 months	870	Retracted, sclerosed leaflets	"Pin-point" opening to right coronary
J. R.	♂	White	35	Toolmaker	1 year	810	Destruction of entire noncoronary and part of right coronary leaflets	
Chas. D.	♂	White	42	Real estate dealer	1 year	650	Primary ring dilatation	Fusiform dilatation of aorta
F. R.	♂	Black	39	Rooming house proprietor	9 weeks	700	Marked sagging of leaflets	Right coronary partially occluded
V.	♂	White	45	Chiropractor	16 months	1,000	Retracted leaflets, greatly thickened at free margin	Marked simple arteriosclerosis of aorta
Wm. M.	♂	Black	39	Musician	4 months	900	Primary ring dilatation	Saccular aneurysm of ascending aorta
M. E.	♂	White	37	Woodworker	7 weeks	650	Thickened and retracted leaflets	
J. L.	♂	White	62	Sailor	6 months	800	Leaflets thickened and rigid	Diffuse dilatation of aorta, with marked simple arteriosclerosis
V. W.	♀	Black	44	Housewife	1 year	525	Sclerosis and slight retraction of leaflets	
S. W.	♂	White	32	Milk distributer	2 years	650	Sagging of leaflets	
S. H.	♂	Black	50	Laborer	Meningitis for 3 weeks	350	Sclerotic leaflets, rolled at free margins	
G. V. M.	♂	White	64	Carpenter	1 year	725	Sclerotic, retracted leaflets	Marked simple arteriosclerosis of aorta; right coronary occluded
G. W.	♂	Black	50	Laborer	3 years (?)	550	Thickened and retracted leaflets	Complete occlusion of right coronary; partial occlusion of left coronary
Geo. W.	♂	White	47	Metal polisher	3 months	675	Thickened, sagging and retracted leaflets	Right coronary completely occluded; left coronary partially so
A. L.	♂	White	63	Teamster	2 years	600	Primary ring dilatation	Marked simple arteriosclerosis of aorta with slight dilatation
A. K.	♂	White	48	Painter	2 years	750	Primary ring dilatation	Aneurysm involving noncoronary sinus of Valsalva

* In this column, ♀ indicates female; ♂, male.

Fig. 1.—The retraction and thickening of the right and noncoronary leaflets. ote the extensive simple arteriosclerosis of the aorta involving the sinuses Valsalva and the plaque spreading the leaflet insertions.

Fig. 2.—The marked thickening and retraction of the right and noncoronary leaflets. Note the rolled appearance of the free borders and the hyaline plaque at the common site of insertion.

APPEARANCE OF THE VALVULAR AREA

In every instance the normal architecture of the valvular area was distorted so as to produce insufficiency at the orifice during diastole. Not a single case was observed in which an actual impediment might have occurred to the passage of blood from the left ventricle into the aorta. Either the ring itself was dilated or the integrity of the leaflets was lost, or, as occasionally happened, both processes were present. In any event, the picture was invariably that of aortic insufficiency and never of stenosis.

HYPERTROPHY OF HEART

With the exception of one case (tuberculous meningitis) all patients had hypertrophied hearts manifested primarily by thickening of the left ventricle. The heaviest of these weighed 1,000 gm.; the lightest 440 gm., with an average weight for the group of 642 gm. Some degree of dilatation of the left ventricle was a consistent finding, extreme in some instances, moderate in others. Occasionally the right ventricle also showed some hypertrophy and dilatation, but never to the same extent as that seen in the left. The gross picture of the heart muscle differed in no way from that seen in hypertrophied hearts from other causes; i. e., hypertension. Varying grades of connective tissue proliferation were noted, either as a diffuse fibrosis, or as patchy cicatrical areas.

ABSENCE OF DISEASE OF OTHER HEART VALVES

No patient was diseased in the other cardiac valves. Although this may have been a coincidence it illustrates a point noted by past writers, namely, that syphilis need hardly be considered a cause of valve disease, except as it attacks the aortic area. So far as we could determine, syphilis appeared to be the sole factor in all cases, as no instance was observed in which a sclerotic syphilitic valve was the seat of another infection.

In addition to the before mentioned features, seen in all cases, we may now consider some aspects of the pathologic changes appearing in individual cases. For example, there was no relation between the severity of the disease process in the aorta and the degree of involvement of the arotic leaflets. In some hearts a high grade of functional insufficiency was obvious, from distortion or actual destruction of the leaflets, with only minimal lesions localized in the suprasigmoid region. In other instances the aorta was extensively diseased; occasionally it was the seat of a diffuse dilatation or a definite aneurysm (three cases in this series), while the leaflets appeared little deformed.

Various deformities of the valve leaflets occurred much more frequently than ring dilatation. Some of the more typical of these are shown in the accompanying photographs, for which I am indebted to

Fig. 3.—The marked destruction of the aortic leaflets; the right coronary is reduced to little more than a fibrous cord while the noncoronary leaflet is completely detached except at the point shown and hangs free in the blood stream.

Fig. 4.—The characteristic sagging of the right and noncoronary leaflets. Note the hyaline plaque at the site of insertion of the two leaflets.

Prof. T. Wingate Todd and his staff at the Anatomical Laboratory. In some instances the leaflets were thick, rigid, or they were reduced in size, both in depth and in width, and appeared as mere fibrous cords (see Figs. 1 and 2). In other cases only the free margin was thickened or curled into a cord-like roll. The most striking example of leaflet destruction (shown in Fig. 3) occurred in the case of J. R., a white man, aged 35. All that remained of the right coronary leaflet was a fibrous fold along the attached border, while the noncoronary leaflet was detached throughout most of its width, and reduced in size to a mere fibrous cord which hung free in the blood stream.

The simplest valve defect noted was a curious sagging of the free border of one or more cusps, as shown in Figure 4. On closer inspection this was found to be due to a hard, pearly, nodular plaque implanted at the site of the common insertion of adjacent cusps. Either by gradual elevation or by extension downward, the plaque had carried with it the valve insertions, which were in some instances situated several millimeters below the normal site of attachment. This resulted in a characteristic drooping of the free margin and in a few cases, particularly in the younger subjects, was the chief defect at the orifice. From the study of the gross picture in several such cases, it appears that syphilis spreading from the aorta toward the heart can attack no more vulnerable spot than the site of insertion of the aortic leaflets.

The syphilitic changes at the root of the aorta were in some cases most severe in and about the sinuses of Valsalva, distorting the structures and frequently involving the coronary orifices. The right coronary was completely occluded in four cases, and in two of these the left was also appreciably narrowed. In two other instances the right vessel opening was partially blocked, so that every fourth case in this series had some degree of coronary obstruction. In this connection, it is interesting to note that in spite of the active disease surrounding their orifices, the coronary vessels themselves were seldom involved. When opened they presented a smooth, normal intima. Exceptions were of course seen in the older patients with intimal arteriosclerosis.

In order to visualize the functional defect at the aortic orifice (the actual leak) more clearly than was possible by simple inspection of the opened specimen, the following procedure was employed: The aorta was cut just below the mouth of the innominate and removed with the heart. A slit large enough to admit two fingers was made in the cavity of the left ventricle, which was washed clean of blood and clots. The heart was supported and the aorta rendered just taut enough that the aortic ring was not artificially distorted. The cavity of the ventricle was illuminated through the slit by a pocket flash light, while water was run into the arota. This simple method illustrated the functional significance of the anatomic change at the aortic orifice.

It was deemed advisable, particularly for teaching purposes, to procure a permanent specimen which would illustrate the defect as observed in some of the more typical cases. After obtaining a view of the aortic area by the simple water method, the cavity of the left ventricle and the aorta were carefully dried. The ventricle was filled with cotton, care being taken not to distend the cavity nor to encroach on the aortic orifice. The heart was supported and hot paraffin was poured into the aorta. Hardening was hastened by carefully lowering the organ into cold water. The aorta was now slit to within a few centimeters of the ring, the paraffin plug was withdrawn and its lower end cast in plaster. After a little practice, models were obtained which quite accurately reproduced the conditions viewed directly by the water method. A model made from a heart showing both ring dilatation and leaflet involvement is reproduced in Figure 5. Models were also made from normal hearts, which showed perfect coaptation of the three leaflets, as shown in Figure 6. In fact, a certain redundancy at the free border of the valves was noted, suggesting that normally the aortic orifice may undergo slight dilatation and yet not be incompetent. This redundancy may serve as a factor of safety under such conditions as vigorous exercise.

Histologic examinations of the aorta and heart were made in every case. In three hearts removed in less than an hour after death, a careful search was made for spirochetes, but not any were found. For the following résumé of the positive microscopic findings in twenty-three of the twenty-five cases I am indebted to Prof. Howard T. Karsner.

MICROSCOPIC FINDINGS

Aorta.—Syphilitic mesaortitis was easily distinguishable in all but four cases, in which the diagnosis was nevertheless clearly established. The destruction of the media was conspicuous in twelve cases, but less marked in eleven.

Heart.—The epicardium showed in varying degree an infiltration of lymphoid, plasma, and endothelial cells in all but six cases. The heart muscle showed in all but one case the changes in the nuclei significant of hypertrophy, i. e., increase in the lateral diameter with squared ends. Cloudy swelling, indicated by diminution or disappearance of transverse striations was found in all but two hearts.

In all instances there was some lesion of the heart muscle, either old or recent. In thirteen hearts there were minute areas in which muscle had disappeared and was replaced by connective tissue. Aside from the cloudy swelling, regarded as of little special significance, hyalinization of muscle, without disappearance of nuclei or other signs of definite fresh necrosis, was marked in two cases, moderate in one, and slight in three. Hydropic infiltration, indicated by definite vacuolization of the muscle fiber cells, was marked in three cases, slight in seven and absent in the others.

Segmentation of notable degree was found in seven instances. Only two hearts failed to show any recent change in the muscle.

The connective tissue showed overgrowth in all cases; this was most marked in the neighborhood of blood vessels except in four cases with only moderate

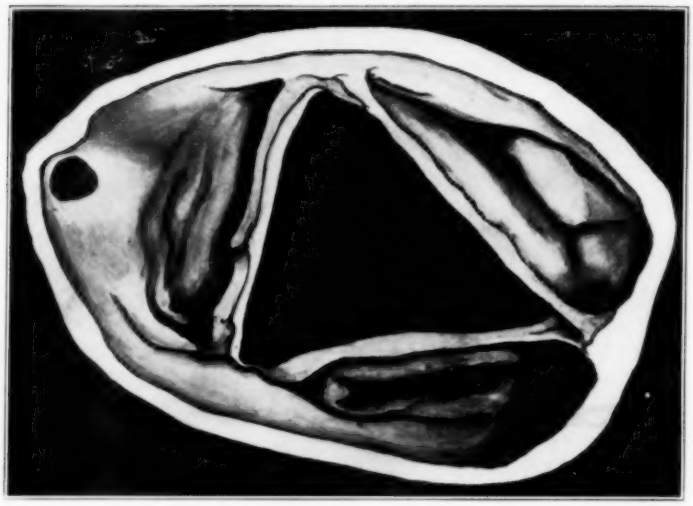

Fig. 5.—A model of the aortic orifice (approximately twice natural size) from a heart showing both ring dilatation and leaflet involvement. The free margins of the thickened and retracted leaflets fail to approximate, leaving the triangular shaped opening shown in the center.

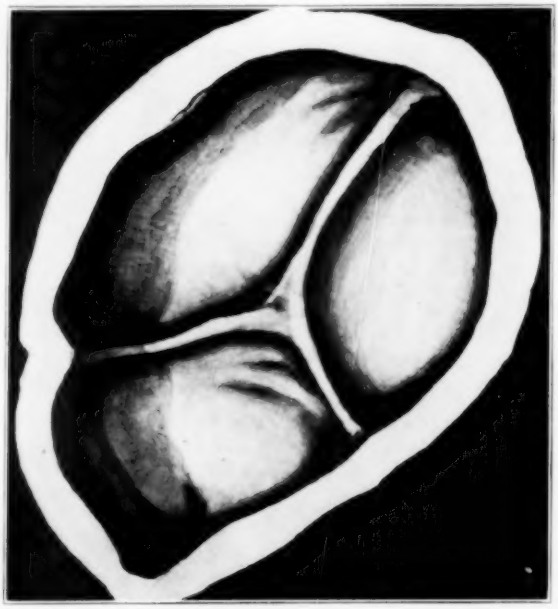

Fig. 6.—A model of a normal adult aortic orifice (approximately twice natural size). Note the perfect coaptation of the three leaflets.

fibrosis. Infiltration of lymphoid and other mononuclear cells was observed in all but six instances. Basic staining of the connective tissue and interfibrillar substance, interpreted as due to mucoid, was found in all but seven cases.

The combination of fibrosis, cell infiltration and mucoid, comparable to the histologic picture of syphilitic myocarditis as described by Warthin, was found in eight instances. Cicatrical types of fibrosis were found in four cases. This was associated with demonstrable intimal sclerosis of the smaller arteries in one case only, where infarcts were also present.

COMMENT

Thus far we have described the clinical and pathologic facts observed in twenty-five proved cases of syphilitic aortic insufficency. An attempt will be made to correlate these facts, and where the evidence warrants, to suggest certain deductions whose final confirmation will require a longer study of more abundant material.

Mention was made of the fact that the first symptoms noted by the majority of patients were those referable to myocardial impairment, i. e., shortness of breath and palpitation on exertion. Although syphilitic mesaortitis was demonstrated at necropsy in every case, the symptoms ordinarily attributed to aortitis (substernal pain and oppression, anginal attacks, a vice-like constriction about the chest, etc.) were conspicuously absent. No doubt some patients gave inaccurate accounts or perhaps disregarded their early symptoms, but so far as could be determined the majority had no symptoms, at least none which in any way interfered with their daily occupation, while the disease was confined to the aorta alone. This observation is difficult to reconcile with the views of Allbutt, Wenckebach, and others, on the dependence of angina pectoris upon aortitis. In discussing this subject Allbut[1] writes: "No cause of angina comes more clearly into view than syphilis." Whether the absence of early symptoms of aortitis may be ascribed to the nervous organization of the type of patient studied, mostly of the laboring class and approximately 50 per cent. negroes, is an interesting question.

The progressive heart failure seen in this group of patients was sufficiently striking compared to other types of heart disease, to merit some consideration of the factors involved in the heart's exhaustion. Twenty patients failed to recover from their first cardiac breakdown. One clear reason for this is the fact that they did not seek medical attention until frank signs of circulatory failure appeared. A study of the necropsy findings, however, suggested that other factors may play an important part in determining the prognosis in this disease.

Syphilitic involvement of the aortic area produces a functional insufficiency at the valve orifice, either by dilatation of the ring or destruction and distortion of the valve leaflets, while a combination of the two

1. Allbutt, Clifford: Diseases of the Arteries Including Angina Pectoris, Vol. II. London, The MacMillan Co., 1915, p. 422.

processes is frequently seen. In any event a leak in diastole occurs, and while this is still small, perfect compensation may be established. But from the very nature of the pathologic changes, the functional lesion tends to be a progressive one, and, developing rapidly, it throws an insuperable burden on the heart which cannot keep pace in establishing compensation.

We have found from inspection by the water method, and from casts made in several cases, that as much as one-half or even more of the total area of the aortic orifice may be rendered insufficient by syphilis, and important from the functional standpoint is the fact that the actual leak occurs in the very center of the stream. Under these circumstances it seems probable that a considerable quantity of blood must actually regurgitate into the ventricle during diastole. Another important factor bearing on the heart's capacity to compensate is the interference with the coronary circulation. One out of four cases in this series had some degree of coronary occluson.

Narrowing of the coronary openings apparently takes place gradually in syphilis, thereby affording time for the development of collateral circulation between the right and left vessels; otherwise it would be difficult to explain the hypertrophy attained by some hearts showing complete occlusion of the right coronary artery with appreciable narrowing of the left (two instances in this series). Oberhelman and LeCount [2] have recently emphasized this point. They believe, from their roentgen-ray studies of the coronary circulation in normal and pathologic hearts, that the extent of the anastomos is between the two vessels is not a matter of age as taught by Gross [3] and others, but is determined in part by the rapidity with which the occluding process develops. Important as this compensatory anastomosis may be, it must ultimately fail in the face of the progressive coronary narrowing which occurs in syphilis.

So far as function may be influenced by anatomic change, it is clear that syphilis at the arotic area is a particularly grave lesion, destroying the integrity of the leaflets on the one hand, and impairing the blood supply to the heart on the other. Singly or in combination these impediments must seriously handicap the heart, and disposed by their nature to progress, they appear to be the most important factors determining prognosis in syphilitic aortic insufficiency.

It was not possible to determine the functional significance of the myocardial changes found in these cases. In eight instances the picture

2. Oberhelman, H. A., and LeCount, E. R.: Variations in Anastomosis of the Coronary Arteries and Their Sequences, J. A. M. A. **82**:1321 (April 26) 1924.

3. Gross, Louis: The Blood Supply to the Heart in its Anatomic and Clinical Aspects, New York, Paul B. Hoeber, 1921.

was that which Warthin [4] attributes to latent syphilis; in fifteen others the changes in the muscle were indistinguishable from those frequently found in hypertrophied hearts from other causes. Certainly in the majority of cases the amount of apparent histologic damage seemed quite insufficient to explain the progressive myocardial failure observed clinically.

SUMMARY

A series of twenty-five patients with syphilitic aortic insufficiency was observed clinically, and the diagnosis confirmed by postmortem examination in every instance. The anatomic changes found in all cases were: (1) syphilitic mesaortitis with extension of the process to the aortic area causing insufficiency at the orifice, and (2) hypertrophy and some degree of dilatation of the heart, chiefly of the left ventricle. One case in four had some grade of coronary occlusion. It was suggested that the progressive widening of the aortic orifice, either from leaflet involvement or ring dilatation, and occlusion of the coronary arteries are the chief factors responsible for the relatively short duration and uninterrupted progression of the heart failure observed in these patients. The histologic changes in the heart muscle were similar to those frequently seen in hypertrophied hearts from other causes. To attribute these changes to latent myocardial syphilis seems unwarranted by the evidence afforded by this series of cases.

4. Warthin, A. S.: The New Pathology of Syphilis, Harvey Lectures, 1917-1919, p. 67-96.

RELATIONS BETWEEN GASTRIC ACHYLIA AND SIMPLE AND PERNICIOUS ANEMIA*

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INTRODUCTION

Fenwick [1] was the first to demonstrate the occurrence of gastric achylia in pernicious anemia; he thought that this might be the cause of the anemia, but emphasized the atrophy of the gastric mucosa. The discussion which followed, therefore, dealt mainly with this atrophy, and when it was found that achylia might be present without atrophy Fenwick's hypothesis lost ground and both anemia and achylia were generally considered coordinated phenomena due to some toxic influence. At the International Congress of Medicine in London (1913) one of us (K. F.) again put forward the hypothesis that the anemia frequently found with achylia gastrica was a secondary phenomenon produced by the lack of gastric secretion even though no atrophy could be demonstrated. In support of this theory he described three cases of pernicious anemia, in which achylia and normal hemoglobin had been found from three to nine years before the onset of the symptoms of anemia. He also stated that not only pernicious anemia, but also a simple anemia of chlorotic type might occur associated with gastric achylia. Later different authors have described cases of pernicious anemia in which achylia was found long before the beginning of the anemia (Kuttner; Cobet and Morawitz; Levine and Ladd; Bie; Hunter [2]). The theory has recently been supported by Hurst.[3]

FREQUENCY OF GASTRIC ACHYLIA IN PERNICIOUS ANEMIA

In a former paper Faber and Bloch [4] presented a series of thirty cases of pernicious anemia, all except one showing achylia.

According to Finnish observers a gastric achylia is frequent in bothriocephalus anemia, but not nearly so frequent as in idiopathic pernicious anemia; for more than 25 per cent. of the cases of anemia due to tapeworm showed a normal acidity of the gastric contents.

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* From the medical clinic of the University of Copenhagen.

1. Fenwick, S.: Lancet **2**:78, 1870; **2**:1, 39, 77, 1877.

2. Kuttner, L.: Spez. Path. u. Therap. **5**:679, 1914. Cobet, R., and Morawitz, P.: Ztschr. f. ang. Anat. **6**:244. Levine, S. A., and Ladd, W. S.: Bull. Johns Hopkins Hosp. **32**:254 (Aug.) 1921. Bie, V.: Lancet **1**:631, 1922. Hunter, Charles: Canad. M. A. J. **13**:38 (Jan.) 1923.

3. Hurst, S. A.: Lancet **1**:111 (Jan.) 1923.

4. Faber, K., and Bloch, C. E.: Ztschr. f. klin. Med. **40**:98, 1900.

Throughout a long period of observation we have seen only four cases of pernicious anemia with normal gastric secretion. The total number of patients with pernicious anemia treated in the clinic between 1907 and 1922 was fifty-four. Achylia was demonstrated in forty-seven cases; three for various reasons were not subjected to a test meal, while four, as before mentioned, showed the presence of free hydrochloric acid. Disregarding the patients not examined we found achylia in 92 per cent. of our cases.

The symptoms and blood picture in these four patients, the histories of which are given at the end of the paper, are so characteristic that they cannot be distinguished from ordinary pernicious anemia.

This, of course, does not settle the question whether achylia, when found, is of pathogenic importance for the anemia; it only means that there must be other possible causes. As already pointed out pernicious anemia can occur without achylia in patients harboring the bothriocephalus tapeworm; it is true that in the pernicious anemia of pregnancy, where the blood picture may be quite similar to that of idiopathic pernicious anemia, achylia may be absent. Levine and Ladd conclude from their series that it is doubtful whether cases without achylia should be classified as pernicious anemia, and that such anemias ought to be considered as probably due to some definite cause. One must inquire whether any etiology could be demonstrated in our four cases. In the literature are reported cases of pernicious anemia in syphilis. Our first patient had an untreated syphilitic infection, but the anemia did not respond favorably to antisyphilitic treatment. In the other three cases there were absolutely no etiologic factors to be found, not even the possibility of a syphilitic infection as the cause. We must then admit that the cause in these cases is entirely obscure, and we may pass to a consideration of the relation between pernicious anemia and achylia when the latter is present.

ACHYLIA PRECEDING PERNICIOUS ANEMIA

It is generally recognized that many patients with pernicious anemia have suffered from gastro-intestinal symptoms for years before the onset of anemia, but this is no proof that achylia precedes anemia unless an examination has shown at some time achylia associated with normal blood findings. This, or at least normal hemoglobin, has been demonstrated in four patients whose histories are given at the end of the paper.

The diagnosis of pernicious anemia in these patients was well supported and was confirmed by necropsy in two of the cases. The achylia was demonstrated from three to twelve years prior to the onset of the anemia, and a normal hemoglobin percentage was found in the early determinations. Levine and Ladd published in 1921 three cases in which

achylia was found long before clinical anemia supervened. These observations show at least that the achylia cannot be attributed to the anemia, although it may be a factor leading to anemia.

In connection with the latter hypothesis it is interesting to note the observations of Hartman,[5] who saw pernicious anemia develop two or three years after complete gastrectomy. This would tend to show that the anemia cannot be due to the diseased stomach, but that the cause is to be sought in the intestines, the contents of which are altered by the lack of gastric digestion whether this be brought about by achylia or by complete gastrectomy.

A further support of this explanation is found in instances of pernicious anemia arising in association with chronic intestinal obstruction, which were first reported by Faber[6] (1895); later Meulengracht[7] was able to collect data on eight such cases.

In oriental sprue, Dutch observers have frequently found an anemia which could not be distinguished from idiopathic pernicious anemia; this also may be due to disturbed intestinal digestion.

ACHYLIA GASTRICA AND SIMPLE ANEMIA

In a paper by Faber[8] (1923) there was given a statistical review of 207 cases of achylia in which the blood had been examined. Twenty-two of these patients suffered from genuine pernicious anemia. Thirty-seven of the remaining 185 patients had hemoglobin below 65 per cent. and fifteen of the thirty-seven below 50 per cent. These anemias were of the simple chloro-anemic type. A simple anemia, even when the rather low after limit of 65 per cent. hemoglobin is used, is a not infrequent finding in association with achylia. This anemia is of a rather benign character and transition to pernicious anemia has not been observed. While the anemia is not lethal, it is somewhat refractory toward treatment and tends to recur. The most successful treatment in these cases appears to be large doses of iron (from 0.5 to 1 gm. of reduced iron U. S. P. three times a day). The anemias occur in both sexes and at all ages and have not a tendency to spontaneous or permanent recovery.

In order to investigate the frequency of this complication we have for a period of several years subjected all our achylia cases to a careful blood examination. Patients with cancer, tuberculosis and pernicious anemia were excluded. As achylia we include the patients who at repeated examinations with Ewald's test meal showed no reaction to Boas' reagent and Congo red and poor chymification of the gastric con-

5. Hartman, H. R.: Am. J. M. Sc. **162**:201 (Aug.) 1921.
6. Faber, K.: Berl. klin. Wchnschr. **34**:643, 1897.
7. Meulengracht, E.: Acta Med. Scand. **56**:432 (April) 1922.
8. Faber, K.: Berl. klin. Wchnschr. **1**:958, 1913.

tents. The blood was examined for hemoglobin, red blood cells and white blood cells and the index was calculated. Stained dry films were carefully examined for the changes found in pernicious anemia. Differential counts were not made in all cases, but frequently a relative lymphocytosis was noted. Neither the leukocyte count nor the dry film findings are noted in the tables given at the end of the paper, since the changes found were generally slight (anisomicrocytosis) and never suggestive of pernicious anemia. Before proceeding further we shall give the normal figures with which these results are to be compared.

In agreement with Bie and Möller's [9] earlier findings in this clinic, Gram and Norgaard [10] found the normal values for hemoglobin, red blood cells and color index given in Table 1.

As a result of quadruplicate counts and standardized technic the ordinary, not inconsiderable, error in the cell count was reduced, so that the index varied very much less than under ordinary clinical con-

TABLE 1.—*Normal Values for Hemoglobin, Red Blood Cells and Color Index*

	Men			Women		
	Hemoglobin, per Cent.	Red Blood Cells, Millions per C.Mm.	Index	Hemoglobin, per Cent.	Red Blood Cells, Millions per C.Mm.	Index
Maximum	118	5.91	1.02	102	5.05	1.04
Minimum	96	4.85	0.99	88	4.36	0.97
Average	105	5.45	1.00	94	4.65	1.01

ditions. The mean error in the hemoglobin determinations (with ten readings of each dilution, in the Autenrieth colorimeter) even under ordinary clinical conditions is in our experience only from 0.9 to 1.1 per cent. hemoglobin, and in these observations all of the determinations were made by the same observer.

We have considered men whose hemoglobin was less than 96 per cent. and women with less than 88 per cent. as anemic. It is, therefore, necessary to consider the men and women separately. Our material, the findings on which are detailed at the end of the paper, consists of ninety cases which we divide into the following groupings: uncomplicated achylia (sixty-three cases), achylia in exophthalmic goiter (fourteen cases) and achylia in chronic polyarthritis (thirteen cases).

1. Uncomplicated achylia (twenty-one men and forty-two women). This first and most important group consists of patients admitted to the wards for various gastro-intestinal troubles and in which complete achylia was found. A careful examination and the later history excluded cancer.

9. Bie, V., and Möller, P.: Arch. d. mal. du cœur. **15**:177 (April) 1922.

10. Gram, H. C., and Norgaard, A.: Relation Between Hemoglobin, Cell Count and Cell Volume in the Venous Blood of Normal Human Subjects, Arch. Int. Med. **31**:164 (Feb.) 1923.

A very considerable proportion of these patients (36.5 per cent.) were anemic, many of them markedly so.

In cases with normal hemoglobin the color index fluctuated around 1 while the index in the anemic cases nearly always was decreased. In the more pronounced cases the microcytosis was clearly visible in the stained films.

2. Achylia in exophthalmic goiter (one man and thirteen women). In exophthalmic goiter achylia is so generally encountered that we do not possess a control material allowing us to say whether this disease, per se, causes an anemia.

Anemia was found in 36 per cent. of these cases, but it was never very severe. In this group also the index tends to be lower in the anemic cases than in those with a normal hemoglobin percentage.

3. Achylia in chronic deforming polyarthritis (two men and eleven women). Achylia is a very frequent finding in this disease, but only our cases with achylia have been studied hematologically.

In this group anemia was even more intense and frequent, being found in 69 per cent. of the cases. We also observed the same tendency to low index in the anemic cases. The greater frequency of anemia in this disease may be due to other factors tending to produce anemia.

Considering all three groups as one we find among ninety cases of achylia thirty-seven (or 41 per cent.) which showed hemoglobin below the lowest normal values established in our clinic. This anemia is often slight but may reach values as low as 45 per cent. of hemoglobin in men (index, 0.6) and 34 per cent. in women (index, 0.5).

The anemia was distinctly more frequent in women than in men, and most of the severe cases occurred among the former. As to the character of the anemia, it was nearly always pronouncedly microcytotic with a low color index. A marked increase of the index was never observed; the cases showing a slight elevation of index above 1 showed normal figures on repeated careful examination.

While the cases with normal hemoglobin showed absolutely normal red cells in the dry films, the preparations from anemic patients often showed a decided anisomicrocytosis. Evidence of forced regeneration (polychromatophil, reticulated or nucleated reds) was found only during treatment with large doses of iron, never in the untreated cases.

Megalocytes or megaloblasts were never observed, in spite of careful search with the ocular micrometer.

Concerning the leukocytes it need only be mentioned that the absolute number was normal or slightly low. Differential counts were not performed on all cases, but frequently showed a relative lymphocytosis, especially in the cases of exophthalmic goiter.

Observations on four cases of pernicious anemia showing normal gastric secretions are presented.

REPORT OF CASES

CASE 1.—A. W., a woman, aged 25, unmarried, was admitted to hospital Oct. 28, 1919. Her family history was negative except that a sister was said to have had anemia for a time. There were no previous significant diseases except for grip in November, 1918; since then the patient had been pale and tired. In the three months before admission there was increasing pallor and shortness of breath.

Physical Examination.—Extreme waxy paleness was noticed, although the patient was well nourished. There were several small hemorrhages in the retina. There were no clinical signs of syphilis. Wassermann reaction was strongly positive at three successive determinations.

Ewald test meal (one hour) was given October 27 to the amount of 106 c.c. Boas reagent revealed traces of free hydrochloric acid. The free acidity with Congo red paper, 31. The total acidity with phenolphthalein, 56. There was no slime. Chymification was good. November 11, an Ewald test meal was given. Boas reagent 20.* Free acidity with Congo red, 35.* Total acidity with phenolphthalein, 50.* There was no slime and chymification was good.

There was no blood or parasite eggs in the feces. In the middle of November a sore throat developed, at which time a small ulcer was found on the right tonsil. Smears from this showed fusiform bacteria but no spirochetes.

TABLE 2.—*Blood Examination*

Date	Hemoglobin, per Cent.	Red Blood Cells Millions per C.Mm.	Index	Leukocytes, per C.Mm.	Plasma Color (Meulengracht)	Platelet Count per C.Mm.	Stained Film
10/28	29	1.05	1.4	2,700	3	22,000	Anisopoikilomegalocytosis; no nucleated red
11/ 1	28	0.96	1.5	1,800	2	25,000	A few basophil reds
11/ 8	31	1.07	1.5	1,500	3	41,000	A few basophil and nucleated reds
11/15	36	1.18	1.5	1,800	3	.....	Several nucleated, among which one typical megaloblast
11/21	31	1.27	1.2	2,700	3	23,000	
11/28	38	1.36	1.4	2,500	3	41,000	
12/ 7	33	1.31	1.3	3,800	4	26,000	
12/17	26	0.98	1.3	2,800	..	.....	
12/19	29	0.80	1.25	1,300	...	.....	

There was a very pronounced hemorrhagic diathesis, as a result of which transfusion was only a partial success. There was slight fever now and then. The patient was treated with arsenic in various forms, mercury and potassium iodid.

There was steady deterioration, and the patient died December 24. Necropsy was refused.

Micrometry of the red cells showed (November 8) an average diameter of 8.9 microns. Differential count (November 21): neutrophils, 48 per cent., eosinophils, 3 per cent., lymphocytes, 40 per cent., monocytes, 7 per cent., basophils, 2 per cent. There were no abnormal types of leukocytes. The results of the blood examination are seen in Table 2.

CASE 2.—E. P., a man, aged 64, married, was admitted June 12, 1920. He had been constipated for many years, and had frequent catarrhal infections of nose and throat. Three months before admission the patient had a sudden attack of vomiting and diarrhea. Since then he had been ill, with increasing pallor and weakness.

Physical Examination.—Extreme anemia without perceptible jaundice. Apart from a slight emphysema of the lungs there were no marked changes in the organs. The patient had slight fever now and then.

* C.c. one-tenth normal NaOH per 100 c.c. test meal changes the reaction.

Ewald test meal (1 hour) June 14 and 18. The free acidity with Congo red was 19 and 53. The total acidity with phenolphthalein, 50 and 83. There was no slime. The chymification was good each day.

In spite of treatment the patient became more and more anemic and died August 3. Necropsy disclosed anemia, myocardial degeneration, hypertrophic gastritis and hypostatic pneumonia.

TABLE 3.—*Blood Examination*

Date	Hemoglobin, per Cent.	Red Blood Cells, Millions per C.Mm.	Index	Leukocytes, per C.Mm.	Plasma Color (Meulengracht)	Platelet Count per C.Mm.	Blood Films
6/14	42	1.34	1.6	7,000	5	447,000	
6/21	36	1.04	1.7	9,900	3	453,000	
6/28	28	0.95	1.5	7,500	3	265,000	
7/ 5	22	0.84	1.3	6,700	...	.....	Anisomegalocytosis; no nucleated reds
7/12	17	0.64	1.3	4,200	...	.....	
7/19	16	0.63	1.2	2,500	...	.....	
7/26	26	0.92	1.4	2,400	...	.....	

The differential leukocyte count was normal.

CASE 3.—T. P., a woman, aged 26, unmarried, was admitted Oct. 29, 1920. Her past and family history were negative. Six months before admission there was increasing lassitude, later vertigo and functional dyspnea.

Physical Examination.—The patient was pale with a subicteric tint. The organs were normal except for systolic murmurs over all of the heart valve areas.

Ewald test meal (1 hour) October 21. The free acidity with Congo red, 22. The total acidity with phenolphthalein, 62. There was no slime, and chymification was good.

There was no improvement in spite of treatment with arsenic, iron and transfusion. There was slight fever with a few sudden rises in temperature. The patient died Dec. 16. Necropsy disclosed anemia, hyperplasia of the bone marrow, fatty degeneration of myocardium and liver, pulmonary infarction and bilateral pleurisy.

TABLE 4.—*Blood Examination*

Date	Hemoglobin, per Cent.	Red Blood Cells, Millions per C.Mm.	Index	Leukocytes, per C.Mm.	Plasma Color (Meulengracht)	Platelet Count per C.Mm.	Blood Films
10/21	30	1.14	1.3	9,100	6	45,000	Pronounced anisomegalocytosis; no nucleated reds
10/24	31	1.16	1.35	8,500	6	56,000	As previous; several megaloblasts and monoblasts
10/27	29	0.99	1.45	4,200	6	34,000	
11/ 2	28	0.91	1.6	8,500	...	.....	
11/ 9	25	0.82	1.6	6,200	...	.....	A few megaloblasts
11/21	26	0.71	1.9	5,900	...	.....	

Average diameter of red corpuscles 8.2 microns (October 27). Differential counts (limits in 5 counts): neutrophil, from 83 to 61; eosinophil, from 2 to 0; basophil, from 1 to 0; monocytes, from 6 to 2; lymphocytes, from 34 to 13.

CASE 4.—E. J., a woman, aged 30, unmarried, was admitted Aug. 31, 1920. The patient had always suffered from "chlorosis." Recently the symptoms were aggravated with weakness, vertigo and dyspnea.

Physical Examination.—The patient was very pale with a slight subicteric tint. The heart was located at the left sternal margin of the fourth rib, and

2 inches outside the mammillary line. The second pulmonary sound was accentuated. There were strong systolic murmurs increasing in intensity toward the base of the heart. The spleen was slightly enlarged.

	Ewald Test Meal (1 Hour)				
	Amount, C.c.	Congo red, N/10 Solution of Sodium Hydroxid, C.c. to 100 C.c. Gastric Contents	Phenolphthalein, N/10 Solution of Sodium Hydroxid, C.c. to 100 C.c. Gastric Contents	Slime	Chymification
September 2.....	223	10	40	0	Good
September 9.....	127	40	60	0	Good
October 5.....	86	38	60	0	Good
December 16.....	115	26	48	0	Good

Treatment with arsenic led to rapid improvement to a certain point and the patient was discharged April 12, 1921, somewhat improved. The temperature was normal. The heart changes were not affected by treatment.

TABLE 5.—*Blood Examination*

Date	Hemoglobin, per Cent.	Red Blood Cells Millions per C.Mm.	Index	Leukocytes, per C.Mm.	Plasma Color (Meulengracht)	Platelet Count per C.Mm.	Blood Films
9/12	59	2.04	1.4	3.700	7	160,000	Slight anisomegalocytosis, no nucleated reds, several polychromatophil reds
9/13	82	3.66	1.1	3.400	3	201,000	
9/24	78	3.44	1.1	4.300	...	204,000	
10/ 5	82	3.50	1.2	2.700	2	167,000	
10/18	71	2.88	1.2	2.800	3	.....	
11/ 3	78	3.05	1.3	4.600	..	.....	
3/14/21	88	3.65	1.2	5.200	...	.....	A few nucleated reds, all of the normoblast type

The average diameter of the red corpuscles (November 13) 8.5 microns. Differential count (limits in 4 counts): neutrophil, from 79 to 56 per cent.; eosinophil, from 3 to 1 per cent.; monocytes, from 6 to 2 per cent.; basophils, none; lymphocytes, from 35 to 16 per cent.

FOUR CASES IN WHICH ACHYLIA AND NORMAL HEMOGLOBIN WERE FOUND BEFORE THE ONSET OF PERNICIOUS ANEMIA

CASE 1.—P. L., a man, aged 31, was first examined in 1903. He had a history of cardialgia, irregular bowel movements and painful, red tongue (Hunter's glossitis) for eighteen months. He was not pale. In 1907 the hemoglobin (Sahli) was from 85 to 90 per cent. (equals from 105 to 110 per cent. by the Haldane test). Achylia: Congo red, none; phenolphthalein, from 12 to 20 c.c.* (several test meals). In 1908, several test meals also showed achylia with no reaction to Congo red and phenolphthalein, 6.* In 1910, there was increasing pallor and weakness. The patient was admitted to the clinic in 1911, suffering from extreme anemia, slight jaundice and small retinal hemorrhages. A test meal showed achylia: Congo red, none; phenolphthalein, 27 c.c.* There was no blood in the feces. The patient died May 2, 1911. Necropsy showed universal anemia, fatty degeneration of the organs and megaloblastic degeneration of the bone marrow.

*A cubic centimeter of tenth normal sodium hydroxid per hundred cubic centimeters gastric content changes the reaction.

TABLE 6.—*Blood Examination*

Date	Hemoglobin, per Cent.	Red Blood Cells, Millions per C.Mm.	Color Index
March	28	0.85	1.6
April	22	0.84	1.3
	18	0.85	1.1

CASE 2.—C. K., a man, aged 52, was first examined in 1909 because of cardialgia, anorexia and vomiting. There was no blood in the feces. Test meal: Congo red, none, phenolphalein, 31,* hemoglobin, from 90 to 100 per cent. (equal to from 110 to 120 per cent. Haldane method). In 1910, the hemoglobin was 90 (equal to 110 per cent. Haldane) and in 1911 hemoglobin 90 (equal to 110 per cent. Haldane). In 1912, there was rapid development of anemia symptoms. Complete achylia by test meal (Congo red, none; phenolphthalein, 30).

TABLE 7.—*Blood Examination*

Date	Hemoglobin, per Cent.	Red Blood Cells, Millions per C.Mm.	Color Index
February	37	1.36	1.4
March	42	1.35	1.6
	40	1.39	1.4
	31	1.06	1.5
April	23	0.40	2.9 ?

Leucopenia and several megalocytes of 10-12 microns diameter. The patient died April 17, 1912. Necropsy was refused.

CASE 3.—C. W., a man, aged 44, was first examined in 1902 on account of "heaviness" and oppression in the epigastrium. Complete achylia (figures lost) hemoglobin 95 (Sahli?). In 1910, the anemia began. Hemoglobin ranged between 70 and 54. Achylia (Congo red, none; phenolphthalein, 10). In 1911, the patient was admitted to the clinic. He was pale, with occasional slight jaundice. The spleen was slightly swollen. There was diarrhea, but no blood in the feces. Complete achylia: Congo red, none; phenolphthalein, 24.

TABLE 8.—*Blood Examination*

Date	Hemoglobin, per Cent.	Red Blood Cells, Millions per C.Mm.	Index
September	46	1.78	1.3
December	40	1.30	1.5

Megalocytosis, nucleated reds and leucopenia. The patient was discharged without improvement and died at home, February, 1912.

CASE 4.—J. P., a man, at the age of 49 had rheumatic fever; immediately thereafter a chronic diarrhea developed, which persisted for the remainder of the patient's life. The patient was examined in 1907. Hemoglobin, 100 per cent. The test meal showed complete achylia: Congo red, none; phenolphthalein, 12; pepsin, none.

In 1920, he was operated on for appendicitis. Following this he said he felt tired and dyspneic. The patient was treated for anemia with good results. In December, 1921, his condition became worse and he was admitted to the clinic. The test meal showwed achylia: Congo red, none, phenolphthalein, 20; pepsin, none.

* A cubic centimeter of tenth normal sodium hydroxid per hundred cubic centimeters gastric content changes the reaction.

TABLE 9.—*Blood Examination*

Date	Hemoglobin, per Cent.	Red Blood Cells, Millions per C.Mm.	Index	Leukocytes per C.Mm.	Plasma Color (Meulengracht)	Platelet Count per C.Mm.
12/30/21	73	2.90	1.3	5.700	5	229,000
1/ 9/22	69	2.12	1.6	2.900	4	192,000
.....	..	....	...	.....	..	.....
2/12/22	43	1.13	1.9	2.000	...	.....

Blood films showed anisopoikilomegalocytosis, but not nucleated reds. The patient died in the clinic from a complicating bronchopneumonia. Necropsy showed the typical changes of pernicious anemia with fatty degeneration of the organs.

RESULTS OF BLOOD EXAMINATIONS IN NINETY CASES OF ACHYLIA

TABLE 10.—*Uncomplicated Achylia in Twenty-One Men*

Normal Blood (16 Cases, or 76 per Cent.)				Anemia (5 Cases, or 24 per Cent.)		
	Hemoglobin, per Cent.	Red Blood Cells, Millions per C.Mm.	Index	Hemoglobin, per Cent.	Red Blood Cells, Millions per C.Mm.	Index
	121	5.57	1.1	96	5.24	0.9
	119	5.71	1.0	91	5.15	0.9
	112	5 79	1.0	69	4.16	0.8
	110	5.84	0.9	67	3.72	0.9
	109	5.65	1.0	64	5.13	0.6
	108	5.38	1.0	..	....	...
	108	5.79	0.9	..	...	...
	108	5.24	1.0	..	...	...
	106	4 99	1.05	..	...	...
	105	5.41	1.0	..	...	...
	105	5.49	1.0	..	...	...
	105	5.49	1.0	..	...	...
	104	5.43	1.0	..	...	...
	103	5.22	1.0	..	...	...
	102	5.10	1.0	..	...	...
	101	4.95	1.0	..	....	...
	98	4.99	1.1	96	5.24	0.9
Max.	121	5.84	0.9	64	3.72	0.6
Min.	98	4.95	1.0	77	4.68	0.8
Aver.	107	5.11				

TABLE 11.—*Uncomplicated Achylia in Forty-Two Women*

Normal Blood (24 Cases, or 57 per Cent.)				Anemia (18 Cases, or 43 per Cent.)		
	Hemoglobin, per Cent.	Red Blood Cells, Millions per C.Mm.	Index	Hemoglobin, per Cent.	Red Blood Cells, Millions per C.Mm.	Index
	123	6.07	1.0	87	5.12	0.85
	107	5.66	0.9	86	5.10	0.8
	105	5.16	1.0	86	4.32	1.0
	105	4.59	1.1	84	4.92	0.9
	104	4.80	1.1	83	4.01	1.0
	104	4.82	1.1	82	4.67	0.9
	103	5.16	1.0	80	5.38	0.7
	102	5.23	1.0	75	4.57	0.8
	101	4.66	1.1	74	3 82	1.0
	101	5.66	0.9	70	4.25	0.8
	100	4.93	1.0	69	4.20	0.8
	98	4.92	1.0	68	4.98	0.7
	98	5.06	1.0	65	4 72	0.7
	97	6.44	0.75	61	5.41	0.6
	97	5.23	0.9	55	3.95	0.7
	96	5.10	0.9	52	3.52	0.7
	96	4.50	1.1	44	2.98	0.7
	94	4.65	1.0	34	3.64	0.5
	93	5.00	0.9	..	..	...
	92	4.49	1.0	..	...	..
	91	4.97	0.9	..	...	..
	91	4.67	1.0	.	....	..
	90	4.75	0.95	..	....	..
	89	5.45	0.8	..	....	...
Max.	123	6.44	1.1	87	5.41	1.0
Min.	89	4.49	0.75	34	2.98	0.5
Aver.	99	5.08	1.0	70	4.42	0.8

TABLE 12.—*Achylia in Chronic Deforming Polyarthritis in Two Men and Eleven Women*

	Men					
	Normal Blood (1 Case, or 50 per Cent.)			Anemia (1 Case, or 50 per Cent.)		
	Hemoglobin, per Cent.	Red Blood Cells, Millions per C.Mm.	Index	Hemoglobin, per Cent.	Red Blood Cells, Millions per C.Mm.	Index
	119	6.11	1.0	92	5.27	0.9
	Women					
	Normal Blood (3 Cases or 27 per Cent.)			Anemia (8 Cases or 73 per Cent.)		
	98	4.93	1.0	84	4.98	0.8
	92	4.64	1.0	83	5.34	0.8
	92	4.37	1.1	81	4.62	0.9
	..	....	...	80	4.41	0.9
	..	....	..	78	4.73	0.8
	..	....	...	75	4.99	0.75
	..	...	...	49	4.41	0.6
	..	....	..	44	4.26	0.5
Max.	98	4.93	1.1	84	5.34	0.9
Min.	92	4.37	1.0	44	4.26	0.5
Aver.	94	4.65	1.0	71	4.72	0.8

TABLE 13.—*Achylia in Exophthalmic Goiter in One Man and Thirteen Women*

	Men (Anemia)					
				Anemia		
	Hemoglobin, per Cent.	Red Blood Cells, Millions per C.Mm.	Index	Hemoglobin, per Cent.	Red Blood Cells, Millions per C.Mm	Index
	...	....	...	87	4.93	0.9
	Women					
	Normal Blood (9 Cases, or 69 per Cent.)			Anemia (4 Cases, or 31 per Cent.)		
	109	5.61	1.0	77	4.09	0.9
	106	5.88	0.9	76	4.57	0.8
	104	6.06	0.9	75	4.10	0.9
	101	4.97	1.0	75	4.61	0.8
	100	5.52	0.9	.	..	...
	91	5.27	0.9	..	....	...
	91	4.91	0.9	..	.. ..	...
	91	4.71	1.0	.	....	...
	89	4.37	1.0	..	.. .	...
Max.	109	6.06	1.0	77	4.61	0.9
Min.	89	4.37	0.9	75	4.09	0.8
Aver.	98	5.26	0.9	76	4.34	0.9

SUMMARY

1. Gastric achylia is usually found in pernicious anemia. It is sometimes missing and four such cases are described.

2. In four cases, the histories and examination of which are given, gastric achylia and normal hemoglobin were demonstrated as long as twelve years before the onset of pernicious anemia.

3. The results of hematologic examination in ninety cases of gastric achylia are described. It is shown that hemoglobin below normal is present in 41 per cent. of these cases or in 36.5 per cent. of the sixty-three uncomplicated achylia cases. This anemia is of the type of simple anemia and may resemble a chlorosis. It differs from chlorosis by its presence in both sexes and all ages and by its tendency to recur.

A CONSIDERATION OF THE CARDIAC ARRHYTHMIAS ON THE BASIS OF LOCAL CIRCULATORY CHANGES *

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In a recent publication [1] two of us reported the results of two series of experiments on the isolated perfused heart. Based on these studies we have developed the conception that in the development and propagation of the excitatory process in the heart, the p_H of the fluid bathing its tissues is a controlling factor. It is considered that the process of excitation is intimately concerned with changes in the state of equilibrium across the cell membrane. In harmony with the hypothesis advanced by Hermann,[2] Brunings,[3] and Bernstein,[4] and more recently elaborated by Lillie,[5] it is suggested that these changes have to do with alterations in the state of polarization existing at the cell tissue fluid interface. The propagation of the excitatory process by means of adjacent tissue by the action current developed at each excited point constitutes "conduction."

It is the purpose of this paper to indicate the possible application of our conception to the arrhythmias. It is conceivable that normal and abnormal rhythms alike are expressions of the inherent "automaticity" and "conductivity" of different portions of the heart; that the same fundamental explanation should apply to the genesis of both groups. For the purpose of this discussion it is considered expedient to regard all irregularities of cardiac rhythm as due to:

1. Abnormalities of the development of the excitatory process.
2. Interference with its normal propagation, or,
3. A combination of both of these.

The experimental evidence for the control of these processes by variations in the hydrogen-ion concentration of the perfusate will be summarized briefly first. We studied the isolated heart of terrapin and dogs by perfusion methods reported elsewhere. Every precaution was observed to assure accurate composition of the perfusate, to maintain

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1. Andrus, E. C., and Carter, E. P.: Heart **11**:97, 1924.
2. Hermann: Handbuch der Physiol. **2**:194, 1879.
3. Brunings: Arch. f. d. ges. Physiol. **100**:367, 1903.
4. Bernstein: Biochem. Ztschr. **50**:393, 1913.
5. Lillie, R. S.: Physiol. Rev. **2**:1 (Jan.) 1922.

a constant temperature and to supply adequate quantities of oxygen with the perfusing solution. Galvanometric records were taken by direct leads and the R-R and P-R intervals carefully measured. It was found possible to control the rate of the isolated perfused heart, both cold blood and mammalian, by changing only the reaction of the perfusing fluid from p_H 7.0 to p_H 7.8. The limits of the variation of

TABLE 1.—*Terrapin, May 5, 1921. Control of Q-R-S Interval by Variations in the p_H of the Perfusate*

Time	P_H	Record	R-R	P-R Seconds	Q-R-S Seconds
2: 45	7.4	1	1.64	0.60	0.20
2: 46	7.8	..	....	....	....
2: 51	...	2	1.68	0.54	0.16
2: 58	...	3	1.56	0.50	0.16
3: 05	...	4	1.60	0.70	0.16
3: 12	7.1	..	....	...	....
3: 17	...	5	1.82	1.00	0.30
3: 27	...	6	1.60	0.96	0.28
3: 28	7.4	..	....	....	....
3: 33	...	7	1.66	0.80	0.24

the p_H were thus relatively narrow. The more alkaline the perfusate, the more rapid was the rate, and the less alkaline the perfusate, the slower the rate.

The experimental results are illustrated in the tables and figures. Table 1 summarizes an experiment on a terrapin's heart involving change in the p_H of the perfusate. Figure 1 illustrates the characteristic electrocardiographic record of a dog's heart, showing the effect of

TABLE 2.—*Dog, June 1, 1923. Control Rate of Nodal Rhythm by Changes in the p_H of the Perfusate*

Time	P_H	Record	R-R Seconds	Rate	P-R Seconds
2: 45	7.4	1	0.80	75	0.11
2: 47		Auricles cut away		..	....
2: 52	...	2	2.00	30	....
2: 53	7.8	..	....	..	....
2: 55	...	4	0.78	77	....
2: 58	7.4	..	....	..	....
3: 03	...	6	2.20	27	....
3: 05	7.1	...	....	..	....
3: 06	...	7	2.60	23	....
3: 09	7.4	..	....	..	....
3: 11	...	9	1.00	60	....
3: 17	...	10	2.28	26	....

similar variations. The R-R interval changes quickly with such alterations, lengthening in the less alkaline and shortening in the more alkaline fluid. Figure 2 is a graphic summary of a similar experiment. Table 2 describes an experiment in which the heart was following an idioventricular rhythm after all sinus and auricular tissue had been cut away. In this case the rhythm is subject to the same changes in rate following alterations in the reaction of the perfusate. Perfusion with

a solution distinctly less alkaline (p_H 7.0) than the normal (p_H 7.4) resulted in some instances in a total cessation of the heart beat, as shown by the electrical as well as by the mechanical records. This result followed occasionally both with sinus and with the idioventricular rhythms. On return to a solution of p_H 7.4 or 7.8, the beat reappeared almost at once and the rate gradually increased.

It was also possible to control by the same means the rate of propagation of the excitatory process. The figures and tables to which reference

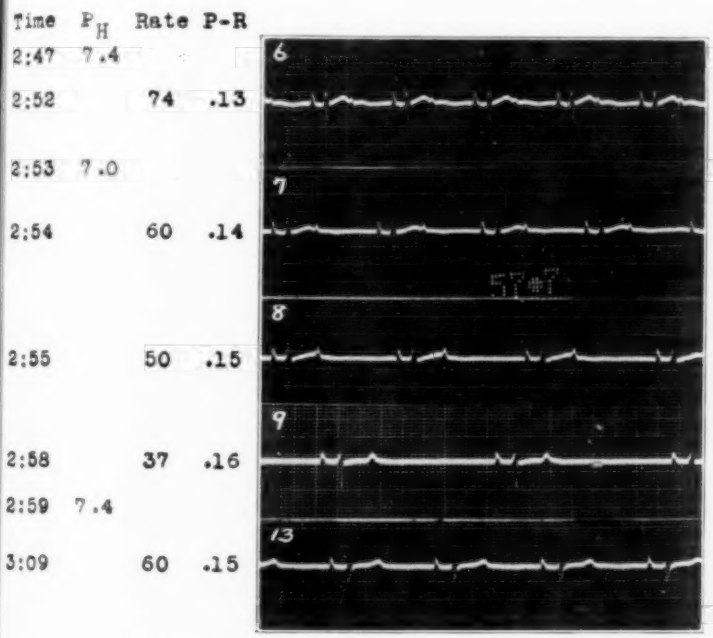

Fig. 1.—Dog, May 11, 1923. The variations in rate and conduction time following changes in the hydrogen-ion concentration of the perfusate.

has been made show that with more alkaline perfusates the rate of conduction, as measured by the P-R interval, is increased; while with less alkaline fluids it is distinctly retarded. This is especially well shown in Table 1 for the cold blooded heart and in Figures 2 and 3 for the mammalian heart. In the former the rate of spread of the excitatory process over the ventricle, as measured by the Q-R-S interval varies with changes in the p_H of the perfusate in the same manner as the P-R interval. Since, as Lewis [6] has shown, specialized conducting tissue is

6. Lewis: Phil. Tr. Roy. Soc. London. **207**:240, 1916.

wanting in the tortoise ventricle, prolongation of the Q-R-S interval in this instance must be regarded as due to an effect on the muscular tissue itself. Figure 3 is from an experiment in which two to one auriculoventricular block was induced by a perfusate with p_H of 7.0 and was later caused to disappear by replacing this with a solution of normal reaction.

From this experimental evidence certain points may be emphasized. Whatever the fundamental process in the development of the cardiac rhythm may be, it takes place more rapidly the more alkaline the fluid

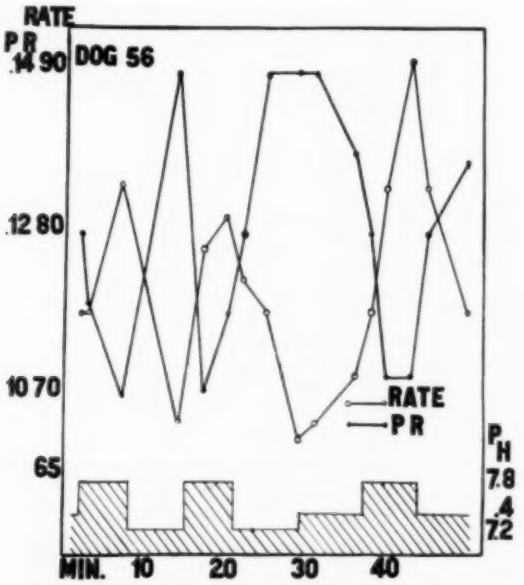

Fig. 2.—Dog, May 9, 1923. Changes in rate and conduction time with alterations in the reaction of the perfusion fluid.

bathing the tissue of the heart as a whole. Moreover, the rate of excitation is distinctly retarded in the presence of fluid of less alkaline reaction and, when a certain degree of diminished alkalinity is reached, it fails to occur. The propagation of the excitatory process undergoes alteration with varying p_H in the same sense as its development. These results suggest that for the development of spontaneous excitation in the heart a certain difference in p_H within and without the tissue must be maintained. That the rate of the rhythm can be varied at will by perfusing with solutions differing only in p_H is further suggestive evidence in this direction.

THE RELATION OF ANOXEMIA TO THE CARDIAC MECHANISM

In attempting to apply the hypothesis which has been developed as the result of experimental work to the clinical irregularities of the heart, some functional basis for the changes presumed to take place must be sought. It would appear that a deficient supply of oxygen due to reduction in the local circulatory minute volume is the essential change which

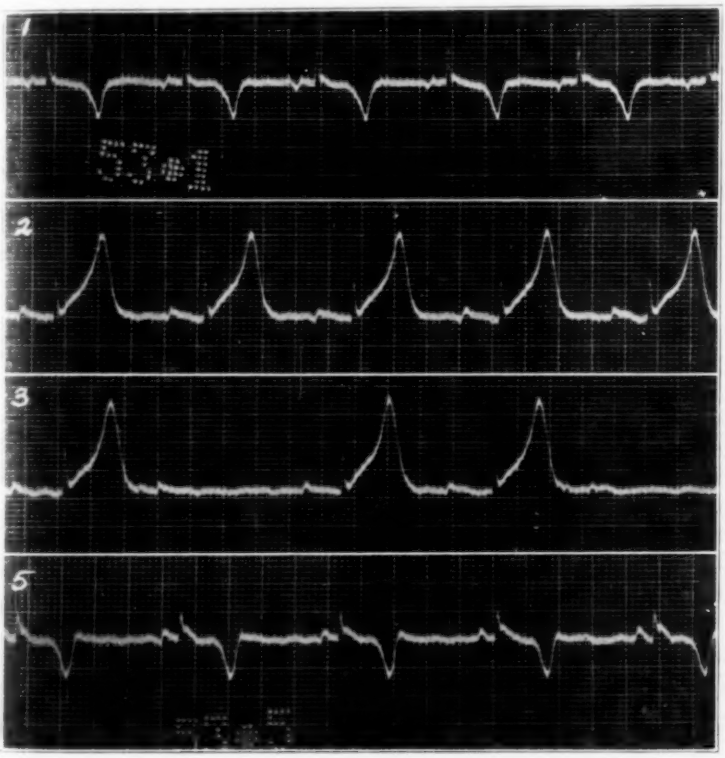

Fig. 3.—Dog, May 3, 1923. The production of delayed conduction and dropped beats by a perfusate of p_H 7.1: 1, p_H 7.4; 2, p_H 7.1; 3 p_H 7.1; 5, p_H 7.4.

may be expected to occur frequently and which might be the underlying disturbance. We have, therefore, examined the meaning of anoxemia from this point of view and gathered together the instances associated with cardiac irregularities. It is not assumed that anoxemia is the sole basis for such disturbances.

Anoxemia may rise through asphyxiation (that is, interference with the supply of oxygen to the pulmonary alveoli) by one means or another,

or through circulatory insufficiency. At first glance it would seem that one is dealing with an exceedingly complicated condition, and this is no doubt true from some points of view. Nevertheless, the fundamental functional disturbance or internal respiration, which is the essential process at issue, may be regarded as unitary. It is well known that the propagation of the excitatory process and the resultant functional response of the tissue to this excitation, for example, contraction, may take place without the immediate consumption of oxygen.[7] When contraction occurs under such conditions, lactic acid, which is the end result of the first phase of the process, accumulates within the cell [8] and later possibly in the fluid bathing the cell. This results in a local increase in the hydrogen-ion concentration. The accumulation of carbon dioxid, which under these circumstances is largely due to the breaking up of alkaline carbonates in the tissue as a result of the increasing acidity,[9] can only produce an enhancement of this effect. The rôle of oxygen consists in the removal of lactic acid in part by oxidation, but for the most part by resynthesis into glycogen by a process not at present thoroughly understood.[10] Hill and Lupton [11] have applied the results of work of recent years in internal respiration in a study of their relation to conditions in men, which results agree admirably with our knowledge of cellular metabolism. They showed conclusively that in exercise an oxygen "debt" is developed through the too rapid accumulation of lactic acid to be removed by the agency of the available oxygen. Normally this accumulated lactic acid is satisfactorily "buffered," mainly by tissue proteins. In the local breakdown of this mechanism the conditions arise which cause an actual local increase in hydrogen-ion concentration to a level above the normal. Such disturbances may take place regionally in relation to the condition of the circulation, and in accordance with the functional activity and buffering power of the tissue. It is evident that the heart, being under the necessity of constant activity, may under pathologic conditions suffer such functional disturbances early and frequently. Skeletal muscles may be rested or their activity limited, but the heart is dependent on its own activity for the constant restoration of normal conditions by the maintenance of its intrinsic circulation.

EXPERIMENTAL ASPHYXIA AND ANOXEMIA

The attention of Lewis and Mathison was directed to the relation of general asphyxia to auriculoventricular conduction by observations of

7. Hill, A. V.: Physiol. Rev. **2**:310 (April) 1922.
8. Fletcher and Hopkins: J. Physiol. **35**:247, 1906-1907.
9. Fletcher and Brown: J. Physiol. **48**:177, 1914.
10. Meyerhoff: Arch. f. d. ges. Physiol. **185**:11, 1920.
11. Hill, A., and Lupton, H.: Quart. J. Med. **16**:135 (Jan.) 1923.

Sherrington [12] and Roaf and Sherrington.[13] As a result, Lewis and Mathison [14] showed conclusively that in cats asphyxiation was soon followed by marked slowing of the sinus rhythm and increase in the conduction time until beats were dropped and finally complete auriculoventricular dissociation occurred. These disturbances always disappeared on the introduction of a normal supply of oxygen, and took place after section of the vagi and after complete atropinization, as tested by stimulation of the nerves. Mathison [15] found that with the vagi intact complete inhibition might occur before heart block appeared. He also extended these observations to dogs. Robinson and Auer [16] produced progressive auriculoventricular block and bundle branch block in rabbits and dogs by inducing anaphylactic shock with horse serum. They also observed indications of a shift of the pacemaker to the auriculoventricular node. Some of their experiments were done after section of the vagi, and their results led them to conclude that the changes were not primarily dependent on vagal action. There are reasons for believing that the mechanism by which anaphylaxis produces these disturbances depends on local circulatory insufficiency. Haggard [17] encountered similar disturbances in dogs, with the respiratory failure which followed carbon monoxid asphyxia. He found that there was a temporary period of auricular inhibition which was prevented by the administration of atropin.

Greene and Gilbert [18] studied the responses of the circulation in men to gradually reduced oxygen tension by the rebreathing method. They found that after a precritical period during which the various compensatory mechanisms dominated the situation, there was great slowing of the rate, shifting of the pacemaker to the auriculoventricular node, and progressive delay in conduction, ending in complete dissociation. Following the discontinuance of the rebreathing the normal mechanism was gradually restored in the reverse direction. These investigators [19] later used the same method of inducing progressive anoxemia in dogs. The same results were secured when the vagi were left intact; but when the vagi were cut, a rapid sinus rate was maintained until the blood pressure manometer failed to record pulse waves, when as a terminal event there was great slowing of the sinus rhythm. This and other considerations led Greene and Gilbert to conclude that the distur-

12. Sherrington: J. Physiol. **38**:375, 1909.
13. Roaf and Sherrington: Quart. J. Exper. Physiol. **3**:209, 1910.
14. Lewis and Mathison: Heart **2**:47, 191011911.
15. Mathison: Heart **2**:54, 1910-1911.
16. Robinson and Auer: J. Exper. Med. **18**:556, 1913.
17. Haggard, H. W.: Am. J. Physiol. **56**:390 (July) 1921.
18. Greene, C. W., and Gilbert, N. C.: Studies on the Response of the Circulation to Low Oxygen Tension, Arch. Int. Med. **27**:517 (May) 1921.
19. Greene, C. W., and Gilbert, N. C.: Am. J. Physiol. **60**:155 (March) 1922.

bances described as occurring in experimental asphyxiation and in men exposed to low oxygen tension were due primarily to "vagospasm" and not to local effect of oxygen want. Two objections may be urged to this conclusion. First, the influence of the sympathetic nerves was not eliminated, and second, it is conceivable that they were dealing with the effect of normal vagus action on abnormal local conditions. This question cannot yet be regarded as settled.

CIRCULATORY INSUFFICIENCY

Most of the suggestive evidence of the relation of oxygen want to clinical cardiac disturbance is in connection with anoxemia due to general circulatory insufficiency. The most striking instance which seems definite is so-called "asphyxial block." Cases are known of auriculoventricular block associated with severe heart failure, in which the normal conduction time has been restored by therapeutic measures which improved the circulation. It is significant that this shortening of conduction time may be accomplished by digitalis.

McCulloch [20] reported in undernourished children, with poor circulation, two instances of abnormally long conduction time which shortened with circulatory improvement. Barach and Woodwell [21] obtained definite improvement of conduction in a case of partial block by the administration of oxygen. Examples of functional interference with conduction through the auriculoventricular bundle are better known. Robinson [22] reported cases showing "aberrant" ventricular complexes following unusually short diastoles, and suggested that the interference with conduction was due to the presence of acid metabolites which were removed by the circulation in the longer pauses. The same author [23] later described a case in which marked heart failure was associated with bundle branch block which disappeared with the improvement following a single large dose of digitalis. Subsequently this patient was seen again with slight heart failure when bundle branch block was present only following short diastolic pauses. Two of Barach's [21] patients showed partial bundle branch block, which disappeared with oxygen therapy. A case similar to that of Robinson, described in the foregoing, is recorded in the files of this laboratory. The patient, when

20. McCulloch, Hugh: Studies on the Heart in Nutritional Disturbances in Infancy, Am. J. Dis. Child. **20**:486 (Dec.) 1920.

21. Barach, A. L., and Woodwell, M. N.: Studies in Oxygen Therapy with Determinations of the Blood Gases, Arch. Int. Med. **28**:367 (Oct.) 1921.

22. Robinson, G. C.: The Relation of Changes in the Form of Ventricular Complex of the Electrocardiogram to Functional Changes in the Heart, Arch. Int. Med. **18**:830 (Dec.) 1916.

23. Robinson, G. C.: The Significance of Abnormalities in the Form of the Electrocardiogram, Arch. Int. Med. **24**:422 (Oct.) 1919.

first seen, had marked congestive heart failure, and the electrocardiographic record showed typical signs of right bundle branch block with a Q-R-S interval of from 0.14 to 0.16 second. After appropriate therapy, including large doses of digitalis, the signs of heart failure disappeared, together with those of bundle branch block. This observation in all its aspects was repeated on the same patient almost a year later. Transient and graded disturbances in bundle conduction in experimental asphyxia have been described by Lewis [24] and are well known clinically.

Recently Gager [25] has described a case of partial heart block in a patient with pericardial effusion. Following treatment, including the removal of the fluid, heart block disappeared completely. The relation of such changes to local circulatory insufficiency is fully discussed, with additional references to the literature.

Electrocardiographic records taken from dying patients furnish us with a series of terminal cardiac disturbances whose basis in most instances is undoubtedly asphyxial. Several observers have reported studies of the events occurring in the hearts of dying patients, showing disturbances of function which agree closely with those encountered in experimental work in which severe anoxemia is produced. Robinson [26] presented a study with electrocardiographic records of the death of seven patients, dying of acute infectious processes without cardiac involvement. Following a preliminary increase in rate, there was consistently a marked progressive slowing of the sinus rhythm. In five patients the conduction time was greatly prolonged and in three of these complete auriculoventricular dissociation occurred. Ventricular fibrillation occurred three times. Halsey's [27] instance of ventricular fibrillation was seen in a patient dying of bronchopneumonia, and preceding this disturbance the records also showed slowing of the sinus rhythm and increase in the conduction time, with the appearance of the signs of partial bundle branch block. Gallavardin [28] reported two instances of long series of ventricular premature beats in dying patients which had not been previously observed. Terminal disturbances of the cardiac mechanism in three patients were described from this laboratory.[29] Much the same changes as those reported by Robinson [26] were found; that is, marked slowing of the rate, increase in the conduction time and in two instances, a shift in the site of the pacemaker, with the development in all three cases of independent ventricular

24. Lewis: Heart **3**:279, 1911-1912.
25. Gager, L. T.: Conduction Changes Accompanying Pericardial Effusion, Arch. Int. Med. **33**:449 (April) 1924.
26. Robinson: J. Exper. Med. **16**:291, 1912.
27. Halsey: Heart **6**:67, 1915-1917.
28. Gallavardin, L.: Arch. d. mal. du. cœur. **13**:207 (May) 1920.
29. Dieuaide, F. R., and Davidson, E. C.: Terminal Cardiac Arrhythmias; Report of Three Cases, Arch. Int. Med. **28**:663 (Nov.) 1921.

rhythms (long series of premature beats, in one case ending in fibrillation). It was suggested at the time that the underlying pathologic physiology of all these disturbances was probably fundamentally the same. In one of the cases there was an interesting example of the presence for a brief time of two noninterfering rhythms in the heart; the first, a much slowed sinus rhythm, and the second an auriculoventricular nodal rhythm (Fig. 3).

CORONARY OCCLUSION

There is one condition in which oxygen want is known to be relatively regional within the heart, namely, interference with the coronary circulation. Ventricular rhythms, including single premature beats, paroxysmal tachycardia and fibrillation, have been frequently encountered as a result of both clinical and experimental obstruction of the coronary arteries. The work of Lewis,[30] Smith [31] and Robinson [32] shows that this series of ventricular ectopic rhythms, or some one of them, very frequently follows experimental ligation of various coronary branches whether the vagi are cut or not.

Robinson and Herrmann [32] observed an instance of paroxysmal tachycardia associated with coronary obstruction, demonstrated at necropsy, and three others in which the diagnosis was made but in which there was no opportunity for its confirmation. Longcope [33] described auricular flutter in four out of nine cases in which coronary occlusion was proved. The sudden onset of auricular fibrillation, associated with definite symptoms of coronary obstruction, was observed in a patient in this clinic. In this instance fibrillation was at first inconstant, being interrupted by periods of normal sinus rhythm and of auricular flutter, but subsequently it became permanent.

The inconstancy of such arrhythmias in clinical cases, in which necropsy findings include coronary obstruction, cannot be entirely explained, but in many cases may depend on the particular coronary vessel involved. Furthermore, the coronary anastomoses now known to exist would account for the absence of these functional disturbances in some instances; while the changes in the cardiac circulation, which Gross [34] has shown to develop with advancing age, throw some light on the age incidence of severe sequelae of coronary obstruction.

In this section an effort has been made to present a summary of the evidence as it exists today, of the relation of oxygen want to cardiac disturbances, together with an interpretation of the local effect of

30. Lewis: Heart **1**:98, 1909-1910.
31. Smith: Arch. Int. Med. **22**:8, 1918.
32. Robinson, G. C., and Herrmann, G. R.: Heart **8**:59 (Feb.) 1921.
33. Longcope, W. T.: J. Iowa M. Soc. **12**:314 (Aug.) 1922.
34. Gross: Blood Supply of Heart, New York, Paul B. Hoeber, 1921.

anoxemia from the point of view of internal respiration. There seems to be no doubt that the primary effect of oxygen deficiency in a contractile tissue is to increase the hydrogen-ion concentration. It has been repeatedly observed that anoxemia pushed to a certain point is associated with: (1) slowing of the sinus rhythm; (2) interference with conduction; and (3) the appearance of ectopic rhythms.

AN INTERPRETATION OF THE CLINICAL DISORDERS OF THE HEART BEAT

Studies of the beat of the heart in situ under ordinary circumstances can only furnish suggestive evidence of the effect of variations in hydrogen-ion concentration on the development and propagation of the excitatory process. A consideration of the pathologic physiology involved leads to the conclusion that such variations during life must always be local except in rare and extreme conditions. It is only in recent years and with refined methods that changes in the p_H of the circulating blood have been detected in other than terminal states. But little is known, as yet, of the relation of such profound general changes to cardiac function. Moreover, abnormalities encountered in the intact heart have to some extent to be interpreted in the light of the control exercised by the extrinsic cardiac nerves. However, it is significant, as Lewis [35] has pointed out, that all of the disturbances in question are encountered in the completely isolated heart. From a general point of view it does not seem that the extrinsic cardiac nerves can play any fundamental rôle in the genesis of the normal or of any abnormal cardiac rhythm, although the action of the vagus and the sympathetic nerves may condition their appearance. Characteristically, the extrinsic nerves exercise but little control over abnormal rhythms, a fact which seems to be correlated with their distribution.

As a profitable basis for their further study and elucidation, it is justifiable to adopt at least tentatively an interpretation of the disturbances of the cardiac mechanism. While the explanation suggested is essentially functional, the part played in many instances by definite anatomic lesions must be borne in mind. At the same time it may be pointed out that in a pathologic process functional disturbance passes gradually into anatomic lesions. Anatomic lesions may interfere with a circulation which in itself is normal.

In the light of the conditions encountered in the clinical observation of cardiac disease, the authors suggest that the conception outlined in the first section of this paper of the nature of the heart beat may assume peculiar significance. The mammalian heart is composed of four types of tissue, nodal tissue, auricular and ventricular muscle, and

35. Lewis, T.: Quart. J. Med. **14**:345, 1921.

Purkinje fibers. It has been shown and most recently emphasized by Lewis [36] that these varieties of tissue normally display quantitative differences in function corresponding to differences in structure. Dale and Thacker [37] have demonstrated on the heart of the frog that the functional limits, as regard hydrogen-ion concentration, vary in different portions of the heart. Similar evidence for the dog's heart has been brought forward by Andrus and Carter.[1] These observations are of interest as indicating quantitative differences in the functional response of various portions of the cardiac tissue to changes in the p_H of the perfusate. The normal heart beat represents the coordinated reactions of the various types of tissue.

It is universally admitted that the property of inherent rhythmicity is developed to the fullest extent in the specific fibers of nodal tissue. To what extent the various other portions of the cardic muscle mass, excluding the specialized tissue, may be endowed with the function of automaticity is not accurately known. It is apparent that under normal conditions such other excitatory centers as may develop lie dormant, giving no evidence of this peculiar property, inherent in all muscle fibers subjected to the proper conditions.[38]

Normally, as Gaskell [39] has indicated, the rhythm of the sino-auricular node commands that of the heart as a whole, because its rate is most rapid. It is as though local conditions were such that, in a certain portion of the S-A node the membrane equilibriums proceed to the critical level most rapidly and thereupon suffer the displacement which constitutes excitation. By virtue of the effect of this local disturbance on the tissue immediately adjacent, the excitatory process is propagated over the auricular muscle toward the ventricle. Just above the A-V ring the "propagated disturbance" meets the specialized tissue of the A-V node, wherein local conditions are such that "conduction" is delayed. From the A-V node the wave of excitation passes to more specialized tissue in which local conditions, again presumably involving the membrane equilibria are such that the local disturbance incident to excitation is adequate as stimulus over a relatively wide reach of fiber; over the Purkinje system the excitatory process is thus transmitted with extreme rapidity.

It is our conception that abnormalities of rhythm, encountered in clinical pathologic conditions, may possibly be explained on the basis of local circulatory deficiency. Such an area of deficient blood supply may conceivably involve two factors; inadequate mechanical removal of the products of tissue metabolism, or an insufficient supply of oxygen in

36. Lewis, T.: Quart. J. Med. **14**:339 (July) 1921.
37. Dale and Thacker: J. Physiol. **47**:493, 1914.
38. Mines: J. Physiol. **37**:1908; Prac. Physiol. Soc. **1**: (May 16) 1908.
39. Gaskell: J. Physiol. **4**:43, 1883.

that area. Under these circumstances one of two conditions may result. An accumulation of waste products (i. e., an increase in hydrogen-ion concentration) in the tissue fluid locally may lead to an area of diminished "conductivity," a localized block. Or, in the event of a more rapid rise in p_H within the tissue, spontaneous excitation may result in that area, and an "heterogenetic" rhythm may arise. The rate of development of such heterogenetic beats and their duration are dependent on the degree of the local change and on the condition of the cardiac tissue as a whole. A minor disturbance may give rise to extrasystoles which may or may not interrupt the dominant rhythm. A more severe disorder may result in a paroxysm of rapid excitations which for a time command the rhythm of the entire heart. If changes occur which result in a decrease in the refractory period of the tissue or in an interference with the propagation of the excitatory process, the circus movement which has been shown to be at the basis of flutter and fibrillation, may appear.

The conception of the development of a local accumulation of hydrogen-ion giving rise to an interrupting cycle or rhythm does not modify the classification of the cardiac rhythms into homogenetic and heterogenetic types as outlined by Lewis.[40] It cannot be too strongly emphasized that the homogenetic rhythm which governs the heart beating in response to the normal excitation, and that which controls the ventricles in the presence of complete auriculoventricular dissociation arise in the specific nodal tissue. All interrupting rhythms are by their nature heterogenetic in the sense that their origin depends on abnormal conditions in the region in which they arise. This view implies the possibility of the development of heterogenetic foci in nodal and specific bundle tissue.

In connection with heterogenetic rhythms it should be emphasized that an effort to show a fixed rate may lead to confusion. It is true that they are usually fast. It can be demonstrated, however, that, with the exception of auricular flutter, the various heterogenetic rhythms do not always have constant rates, although they are more constant than the homogenetic rhythms. Given constant conditions, the rate of development and discharge of the excitatory process may be very exact; the more rapid it becomes the more exactly rhythmic it appears since the demonstrable error in the cycle length is reduced.

SINUS ARRHYTHMIA

We believe that a sinus arrhythmia is determined by the action of the vagus, which so influences the local membrane equilibriums as to result in an irregularity in the discharge of the local excitation. The

40. Lewis: J. Physiol. **4**:321, 1883.

great variation in the rate of stimulus production in the sino-auricular node should be emphasized. Instances of sinus rhythm having a rate as low as 30 have been recorded. It has been shown conclusively that under constant conditions the heart isolated from all sympathetic and vagus connections responds at a constant rate.

NODAL RHYTHM

In the extensive literature dealing with the idioventricular rhythm the subject has been treated in great detail from every possible point of view. There is a wide variation in the rates that may be present in complete auriculoventricular dissociation. It has also been shown that in some instances the idioventricular rhythm may have a slightly faster rate than that governing the auricle. Lea's [41] case of complete heart block, in which during a fall to 51 in the sinus rate the ventricular rate rose to 59, is of interest in this connection. In several instances these faster ventricular rates have been induced by drugs,[42] while in others the development of an idioventricular rhythm has been associated with the influence of the extrinsic cardiac nerves.

Heterogenetic rhythms may arise in the auriculoventricular node at a rapid rate, and may even control the auricular systole through retrograde spread of the excitation wave. On the basis of the hypothesis advanced, the occurrence of a nodal excitation implies the development of some local change within the node giving rise to an excitation which is to be regarded as heterogenetic whether this premature contraction interrupts the rhythm of complete heart block or the normal sinus sequence. That there may exist some correlation between the rate of development of the excitation process in the sino-auricular node and the auriculoventricular node seems not improbable. It is apparently true that in some instances in the presence of an extremely slow sinus rate, the inherent periodicity of the auriculoventricular node is correspondingly reduced. There are in this laboratory records of six persons with normal sinus rhythm, in whom the cardiac rate varies from 34 to 46 a minute. In none of these was vagus stimulation followed by ventricular escape.

As further evidence of the inconstant presence of independent rhythmic foci, reference may be made in some detail to the case

41. Lea: Lancet **1**:1289 (Jan.) 1915.

42. Brown, N. W.: Sino-Atrial Heart Block in a Child, Arch. Int. Med. **24**:458 (Oct.) 1919; Gallavardin; Dufourt and Petzetakis, Arch. d. mal. du. cœur. **7**:1, 1914; Hewlett, A. W.: Heart, **10**:9 (April) 1923; White, P. D.: Ventricular Escape with Observations on Cases Showing a Ventricular Rate Greater than that of the Auricles, Arch. Int. Med. **18**:244 (Aug.) 1916; Wilson, F. N.: The Production of Atrioventricular Rhythm in a Man after the Administration of Atropin, Arch. Int. Med. **16**:989 (Dec.) 1915.

illustrated by Figure 4 *a*, *b*, *c*, and *d*, which affords presumptive proof of the presence of two homogenetic centers dominating at different times the cardiac response, with the occasional occurrence of heterogenetic ventricular beats of a second type. The mechanism involved,

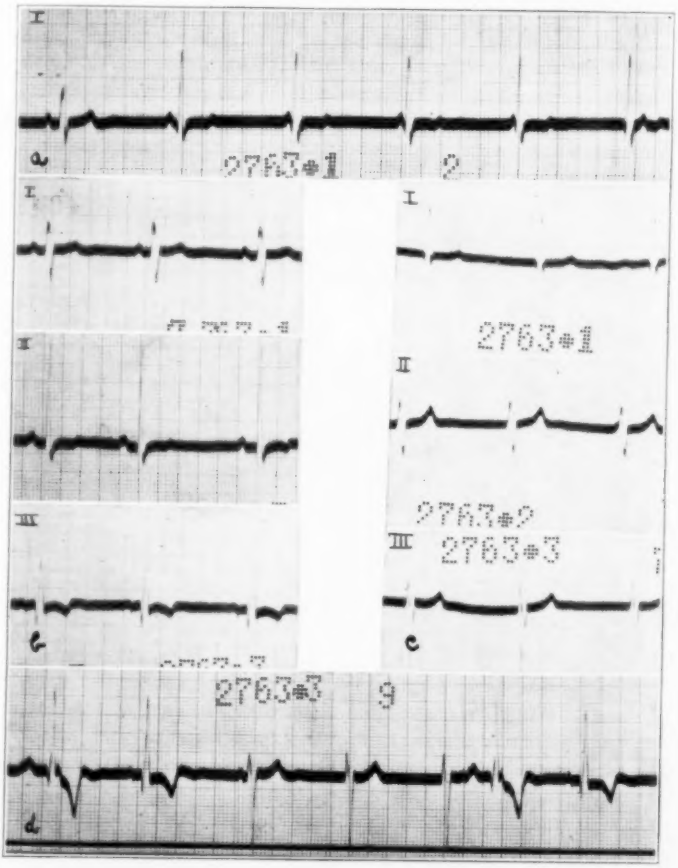

Fig. 4.—*a*, Lead 1. The onset of idioventricular rhythm. *b*, Leads 1, 11 and 111. Normal mechanism of case illustrated. *c*, Leads, 1, 11 and 111. *d*, Lead 111.

as is readily apparent, corresponds in every detail to that seen in the escape of the auriculoventricular node following a progressively slowing sinus rate. In this instance, however, the escape of the subsidiary center is associated, in all three leads, with a ventricular complex that in no way resembles that seen with the normal sinus rhythm. This

subsidiary rhythm can only be interpreted as an escape of the auriculoventricular node, constantly associated with an aberrant ventricular complex; or, as due to the presence of a local rhythmic focus at a slightly lower level, lying probably near the point of division of the main His bundle in closer relation to the left than to the right branch. The constancy of the ventricular complex of the ectopic rhythm, together with the extraordinary persistence of the two alternating rhythms, seems wholly to exclude the view that the ectopic rhythm represents an auriculoventricular nodal rhythm with aberrant complexes. Records of this case over a long period, in the entire absence of any digitalis or other drug therapy, show that there is never the slightest variation in the recorded ventricular complexes associated with the two rhythms. Whenever the sino-auricular rate, as determined by the P-P interval, falls to 1.12 seconds, the ectopic focus asserts itself and continues at times for long intervals, appearing as in Figure 4 *a*, with a gradually lengthening distance between R and P, or as seen in Figure 4 *c*, as a ventricular rhythm with the P waves of the normal sinus rhythm occuring at the same frequency, lost in the ventricular complex of the ectopic beat. This may be interpreted, it is true, during the interval in which the P wave becomes buried, as an auriculoventricular rhythm with but a single pacemaker. With the presence of the P wave, however, the previous interpretation alone seems possible. Assuming even that there is present a constant shift from an idioventricular rhythm to an auriculoventricular rhythm and back, the inference as to the presence of two rhythmic foci is unaffected. No more striking contrast can be imagined than that illustrated by Figures 4 *b* and *c*. Figure 4 *d* illustrates the occurrence of ectopic ventricular beats of a second type, together with two cycles of the normal sinus rhythm and three cycles of the first ectopic rhythm.

It seems certain that the mechanism involved in this case is of the nature of that present in escape of the auriculoventricular node. The unusual features are the regularity with which the ectopic focus asserts itself in relation to the variable sino-auricular rate, the constancy of the form of the ventricular complex associated with the ectopic rhythm and the persistence of the phenomenon of alternation of the two rhythms from hour to hour and week to week during the entire time the person was under observation. It is of interest that the ventricular extrasystoles are always followed by a cycle of the normal sinus rhythm, and that vagus stimulation is without effect on the ectopic rhythm. It is quite impossible to foretell which of the two rhythms may be in control, while during the activity of the subsidiary ventricular focus the sino-auricular rhythm goes on undisturbed at a slightly slower rate, or apparently synchronously for long periods.

PREMATURE CONTRACTIONS

It is significant that it has been possible to induce in the isolated perfused heart, interrupting rhythms, as shown in Figure 5, quite as complicated as the clinical arrhythmia illustrated in Figure 6 (discussed further on), with a disappearance of the irregularity on return to an alkaline perfusate.

The occurrence of extrasystoles having a constant form, can be regarded as evidence of a local automatic focus only when they appear

Fig. 5.—Dog, May 11, 1923. The production of ventricular premature beats by an acid perfusate and their disappearance on return to an alkaline perfusate.

so long after the preceding cycle that they cannot possibly be interpreted as re-entrant waves. That under some conditions premature beats may be due to the re-entry of the preceding excitatory process of the dominant rhythm must be admitted. Although an isolated extrasystole can in no sense be interpreted as evidence of a rhythmic focus, under the conditions defined above it represents a focus of automaticity which may declare itself by continuous cycles arising rhythmically. When single extrasystoles appear from time to time in a person known to have attacks of multiple runs of similar complexes, then and then only can such a single interrupting cycle be considered as representing

a rhythmic focus, though the isolated interrupting cycles are not to be regarded as members of a continuous rhythm. This distinction we believe to be fundamentally important.

In the analysis of the galvanometric curves of clinical cases the interpretation of the location of the abnormal focus is made solely on the difference in form of the interrupting complex from that of the normal rhythm. On this account the interpretation of a sinus extrasystole may remain incapable of proof.[43]

Many observers [44] have published curves illustrating the incidence of single and even multiple premature auricular complexes, which are interpreted as arising nearby or within the sino-auricular node. Of the origin of extrasystoles arising within the auriculoventricular node there is abundant and demonstrable evidence. By analogy it is difficult to question the occurrence of sino-auricular extrasystoles. It seems a justifiable inference that under certain conditions of local circulatory change a focus in the sino-auricular node, other than that giving rise to the dominant rhythm, may develop an excitatory process. Under these circumstances the interrupting focus should be considered as nomotopic but heterogenetic. We believe that it is the development of such foci within the sino-auricular node that results in what has hitherto been described as a "shift of the pacemaker within the sino-auricular node" as in the experimental curves of Lewis' [45] dogs. The vagal mechanism involved in such an experimental shift does not come within the scope of this discussion.

It should be emphasized that it is held by some observers that there is no evidence of the active existence of two rhythms in the same chamber of the heart at the same time. There is, however, evidence supporting the view that at least two foci of automaticity may be present in the same chamber at the same time. In this connection the instance reported by Klewitz [46] is of unusual interest and it is difficult to escape the conclusion based on the published curves, that there were two conflicting

43. Belski: Ztschr. f. klin. Med. **67**:515, 1909; Lohmann: Arch. f. Anat. u. Physiol. (Physiol. Abth.) 431, 1904; Rihl: Deutsch. Arch. f. klin. Med. **94**:286, 1908; Rihl: Ztschr. f. exper. Path. u. Therap. **9**:496, 1911; Ritchie: Quart. J. Med. **6**:47, 1912; Rothberger, C. J.: Klin. Wchnschr. **1**:2150 (Oct.) 1922; Rothberger, C. J., and Winterberg: Arch. f. d. ges. Physiol. **142**:461, 1911; Wenckebach: Arch. f. Anat. u. Physiol. (Physiol. Abth.) Supp. **1**:53, 1908.

44. Carter, E. P., and Wedd, A. M.: Report of a Case of Paroxysmal Tachycardia Characterized by Unusual Control of the Fast Rhythm, Arch. Int. Med. **22**:571 (Nov.) 1918; Klewitz: Centralb. f. Herz u. Gafasskh. **12**:54, 1920; Lewis, Thomas: Mechanism and Graphic Registration of the Heart Beat, London, Shaw and Sons, p. 229, 1920; Wenckebach: Arch. f. Anat. u. Physiol. (Physiol. Abth.) 1, 1907; White, P. D.: Clinical Observations on Unusual Mechanisms of the Auricular Pacemaker, Arch. Int. Med. **25**:420 (April) 1920.

45. Lewis, Meakins, and White: Phil. Tr. Roy. Soc., London **205**:375, 1914.

46. Footnote 44, second reference.

rhythms present in the sino-auricular node during the same period. It is of additional significance in connection with its origin that the heterogenetic rhythm could be abolished by vagal stimulation and, therefore, must have arisen in an area supplied by the vagus.

As evidence of the effects of local or regional changes within the auricle, one has but to recall the frequency with which heterogenetic auricular beats occur, which are capable of interpretation by the character of their recorded curves, by their time relationship to the dominant rhythm and in many instances by the alteration in conduction time.

The occurrence of ventricular premature contractions which fulfil the conditions imposed in the foregoing, offers the simplest proof that the underlying disturbance is essentially a local one. These subordinate heterogenetic rhythms develop at a wide range of periodicity, and under certain conditions the frequency of the subordinate focus may show an apparent relationship to that of the controlling sinus rhythm. The idea that a relationship exists between the normal sinus rhythm and a subordinate rhythmic focus, as evidenced by the occurrence of

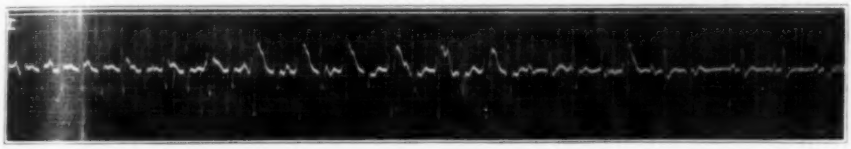

Fig. 6.—Lead 1. Two series of premature beats from different foci. The normal P waves occur independently of the ectopic beats.

extrasystoles at definite time intervals, has been developed in an interesting way by Kaufmann and Rothberger.[47] The recent study by Iliescu and Sebastiani [48] to show that no such relationship can be established does not seem conclusive. The question of the relationship of the ectopic rhythm to the dominant rhythm in the presence of coupled beats is a very difficult one. That the extrasystole is induced by the normal systole, even in those instances in which there is a strikingly constant time interval between the sinus beat and the coupled cycle, has not yet been proved. Under these conditions, however, the question of an alteration in the refractory period of the heart muscle and the possibility of re-entry of the excitation wave must be emphasized. The appearance of the second cycle may be conditioned by the normal cycle but its genesis is determined by regional processes.

An example of three independent rhythmic foci, the normal sinus and two ectopic ventricular rhythms, is illustrated in Figure 6. Each

47. Kaufmann, R., and Rothberger, C. J.: Klin. Wchnschr. **1**:1840 (Sept.) 1922.

48. Iliescu, C. C., and Sebastiani, A.: Heart **10**:101 (April) 1923.

of the two subsidiary foci breaks through at different times with its own periodicity, while the normal sinus rhythm can be spaced throughout the curves uninfluenced by the rate of the heterogenetic centers. The rhythms of these heterogenetic foci are not continuous, nor can their appearance be predicted. Each focus, however, when it does appear, has a rate which tends to be characteristic. Thus the normal sinus rhythm is interrupted frequently by a rhythm arising in the ventricles having a rate of 182, with a duration occasionally of at least 30 cycles. This tachycardia is in turn replaced by a rhythm from a second ventricular center at a rate of 88, while throughout the tachycardias the normal P wave appears at its own inherent frequency of 93.

CIRCUS MOVEMENTS

The "circus movement," which underlies auricular flutter and fibrillation, has a direct bearing on the theory offered in explanation of the genesis of the cardiac beat only in that the functional alterations involved in the establishment of this process are conceivably determined by diffuse circulatory changes of the sort described. Following immediately on the establishment of a circus movement, however, the evidence of the point of origin of the excitatory process is lost. The auricular complexes only afford a measurement of the rate at which the excitatory process, in its spread through the auricular tissue, passes a given point. The theory suggested does not modify in any way the present conception of the evolution of circus movements, but on the other hand aids in our conception of the development of local areas of muscle bundles through which the passage of the excitatory process is delayed. It is important to remember the significance of the refractory period of the heart in connection with re-entrant waves of excitation. The possible effect of a change in the hydrogen-ion concentration on the refractory period of cardiac muscle offers a problem of the greatest significance to the hypothesis advanced. We have frequently observed in experimental fibrillation of the ventricles that there are many local areas of conflicting, re-entering waves quite apart from the chief circus movement. Finally it is important that there is no evidence that a circus movement may not be initiated by the dominant rhythm, its onset being determined by primary changes in the refractory period due to disturbances in membrane equilibria.

SUMMARY

The hypothesis that the "automaticity" of the heart is due to the rhythmic displacement of the membrane equilibria is advanced as applicable to the cardiac arrhythmias. It is suggested that the development of the excitatory process is determined by the difference in hydrogen-ion concentration within the cardiac tissue and in the tissue fluid bathing it.

Normally, the spontaneous development of the excitatory process takes place only in the sino-auricular node; but it may, by a process relatively normal, readily occur, usually at a slower rate, in the auriculo-ventricular node. These mechanisms constitute the homogenetic rhythms. The excitatory process is propagated through the effect of the local disturbance on the membrane equilibria in adjacent tissue, an effect also controlled by the p_H within and without the tissue.

It is further suggested that under pathologic conditions local accumulation of hydrogen ions may develop in nodal tissue or in various other parts of the heart, giving rise to heterogenetic beats or rhythms; the evidence for this is outlined. Re-entrant waves and circus movements may be accounted for by regional or diffuse changes of the same nature. The mechanism by which pathologic changes usually produce these results is a local increase in hydrogen-ion concentration within the tissue, which is due to an insufficient supply of oxygen. On the other hand, a pathologic process which causes a relative increase in the concentration of hydrogen ions in the tissue fluid interferes with the spread of the excitatory process, thereby giving rise to the various forms of "block." The mechanism of these general type of pathologic processes is discussed and experimental and clinical instances suggestive of their operation are described.[49]

49. Since this paper was written, two of us (E. P. C. and F. R. D.) have completed a study, to be reported in detail later, demonstrating that in the perfused dog's heart the refractory period of the cardiac muscle varies with the p_H of the perfusion fluid, being lengthened on the acid side and shortened on the alkaline side of neutrality. Andrus and Drury, in a series of observations soon to be reported, have further demonstrated that when the dog's auricle is perfused with oxygen-free Locke's solution of p_H 7, there results a condition in which the transmission of the excitation becomes progressively slower the farther the wave travels from its point of origin. If such perfusion is continued, partial or complete block may be produced within the auricular muscle itself. Such a condition bears a striking similarity to the phenomenon described in the nerve as "conduction with a decrement."

THE AMINO-ACID CONTENT OF BLOOD IN VARIOUS PATHOLOGIC CONDITIONS

AN ANALYSIS OF ONE HUNDRED AND SIXTY DETERMINATIONS ON ONE HUNDRED AND TWENTY PERSONS *

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Basing the study on an analysis of the results obtained in 160 routine determinations of the amino-acid nitrogen in the blood of 120 subjects, mostly patients with miscellaneous pathologic conditions, an attempt has been made here to correlate the abnormal findings with any diseases with which they might consistently be associated. With reference to conditions in which other investigators have found high figures for the amino-acids of blood, our cases were grouped for separate study in order to show at a glance what our findings have been in these conditions. Finally, the tabulation was studied with a view to ascertaining a possible relationship between retention of urea nitrogen and accumulation of amino-acids in the blood. A small group of amino-acid nitrogen readings from fluids other than whole blood is appended.

Folin,[1] in a group of twelve normal young men, found the average value of amino-acid nitrogen in whole blood to be 6.4 mg. per hundred cubic centimeters, with a maximal reading of 7.8 mg., and a minimal reading of 5.7 mg. In his opinion, the deamination process is so fundamental that one cannot expect to find many pathologic conditions in which the aminonitrogen of the blood filtrates will vary very much from the normal.

In acute yellow atrophy of the liver, the amino-acid nitrogen of the blood was found by Stadie and Van Slyke [2] to be greatly increased. Okada and Hayashi,[3] in 1922, obtained pronounced rises in the blood aminonitrogen in cases of leukemia, the figures being approximately proportioned to the white cell count. In five cases of splenomyelogenous

* From the Clinical Laboratory, United Israel Zion Hospital.

1. Folin, O.: Laboratory Manual of Biological Chemistry, 1922, p. 279, New York, D. Appleton & Company.

2. Stadie, W. C., and Van Slyke, D. D.: The Effect of Acute Yellow Atrophy on Metabolism and on the Composition of the Liver, Arch. Int. Med. **25**:693 (June) 1920.

3. Okada, S., and Hayashi, T.: Studies on the Amino-Acid Nitrogen Content of the Blood, J. Biol. Chem. **51**:121 (March) 1922.

TABLE 1.—*Findings in a Group of One Hundred and Twenty Patients*

Case	Mg. per 100 C.c. Blood Filtrate: Amino-Acid Nitrogen	Mg. per 100 C.c. Blood Filtrate: Urea Nitrogen	Diagnosis
1	17.5	37.5	Cardiac decompensation; myocarditis
2	16.4	15.0	Emphysema
	9.3	15.0	
	5.8	13.6	
3	12.0	42.8	Coronary sclerosis; pulmonary tuberculosis
4	12.0	12.0	Stillbirth; mother eclamptic
5	11.0	171.2	Uremia; nephrolithiasis
	6.8	171.2	
6	10.0	30.0	Diabetic coma
7	10.0	15.4	Colitis
	9.1		
	8.2		
	6.4		
8	9.3		Lobar pneumonia
	8.7		
	8.7		
	8.2		
	5.8		
9	8.7	15.0	Chronic cholecystitis
	7.0	15.0	
10	8.7	20.6	Chronic myocarditis
11	8.7	12.0	Carcinoma of stomach
12	8.5		Infective cholangeitis
	7.0		
	7.0	24.9	
13	8.2		Normal
	7.9		
	7.9		
14	8.2	15.0	Diabetes mellitus
15	8.2	13.4	Diabetes mellitus
	7.3	16.7	
16	8.2	15.6	Cholelithiasis
17	8.2	50.0	Chronic glomerular nephritis; uremia
18	8.2	13.6	Cerebral thrombosis
19	8.2	15.0	Carcinoma of pancreas
20	8.0		Normal
21	7.9		Syphilis of liver
	7.9		
	7.0		
22	7.7	15.0	Cerebrospinal syphilis
23	7.7	15.2	Pyelitis
24	7.6	12.0	Ureteral obstruction
25	7.7		Acute gangrenous appendicitis
26	7.4	14.6	Herpes zoster
27	7.4	17.6	Diabetes mellitus
28	7.4	30.0	Diabetes mellitus
29	7.4		Acute nephritis
30	7.4		Rheumatic fever
31	7.2		Tuberculous pleurisy; osteo-arthritis
32	7.2		Diabetes mellitus
	7.0	15.4	
	5.2		
33	7.2	15.8	Arteriosclerosis; abdominal angina
	7.0	15.8	
	7.0	16.8	
34	7.0	15.0	Coronary sclerosis
35	7.0	15.8	Parturition
36	7.0		Menopause
37	7.0	15.8	Ovarian cyst
38	7.0	15.8	Myocardial insufficiency
	7.0	15.0	
39	7.0		Normal
	6.7		
	6.1		
40	7.0	27.2	Constipation
41	7.0	18.8	Cerebral arteriosclerosis
42	7.0		Chronic colitis
43	7.0		Osteo-arthritis
	6.6		
	6.4		
	6.4		
44	7.0	18.8	Coronary sclerosis
45	7.0	15.0	Multiple myostitis
46	7.0	17.6	Mitral stenosis
47	7.0	13.6	Diabetes mellitus
	6.6		
48	7.0	14.4	Cholecystitis
49	7.0	15.8	Pneumothorax
50	7.0		Hyperthyroidism
51	7.0	15.8	Chlorosis
52	7.0	15.0	Ureteral obstruction

TABLE 1.—*Findings in a Group of One Hundred and Twenty Patients—(Continued)*

Case	Mg. per 100 C.c. Blood Filtrate: Amino-Acid Nitrogen	Mg. per 100 C.c. Blood Filtrate: Urea Nitrogen	Diagnosis
53	7.0	18.8	Auricular fibrillation
54	7.0	21.3	Lobar pneumonia
55	7.0	15.8	Acute infectious arthritis
56	7.0	15.8	Diabetes mellitus
	6.4	18.8	
	5.0		
57	7.0	15.0	Hydronephrosis
58	7.0	15.0	Umbilical hernia
59	7.0		Renal calculus; hydronephrosis
60	7.0	27.2	Food allergy
	7.0		
	7.0		
61	7.0	15.0	Diabetes mellitus
62	7.0		Osteo-arthritis
63	7.0		Osteo-arthritis
	5.6	15.8	
64	6.8	16.7	Pregnancy; epilepsy
65	6.7		Carbuncle
66	6.7		Diabetes mellitus
	5.4	15.8	
67	6.6		Influenzal pneumonia
68	6.6	15.8	Neurasthenia
69	6.6	21.4	Cerebral arteriosclerosis
70	6.6	15.8	Diabetes mellitus; hepatic cirrhosis
71	6.6	27.2	Ureteral obstruction
72	6.6	55.0	Chronic glomerular nephritis; uremia
73	6.6	12.0	Eclampsia
74	6.6		Diabetes mellitus
75	6.6	15.0	Diabetes mellitus
	6.4	15.0	
76	6.6		Acute nephritis
77	6.5	17.6	Typhoid fever
78	6.4	17.6	Acute nephritis
79	6.4	20.6	Hypertrophied prostate
80	6.4		Diabetes mellitus
81	6.4	14.4	Diabetes mellitus
82	6.4	15.8	Ventral hernia; peritoneal adhesions
83	6.4	15.8	Menopause
84	6.4	15.0	Peritoneal adhesions
85	6.4	15.0	Bronchopneumonia
86	6.4	15.0	Diabetes mellitus; acute cholecystitis
	5.8		
87	6.4	15.0	Endarteritis obliterans
88	6.4		Parturition
89	6.4		Diabetes mellitus
90	6.4	17.6	Rheumatic fever
91	6.4	12.5	Rheumatic fever
92	6.4	16.7	Acute polyarthritis
93	6.3	15.8	Cardiac decompensation
94	6.3	15.8	Arteriosclerosis; hepatic cirrhosis; osteo-arthritis
95	6.3	15.8	Myocardial insufficiency
96	6.3		Diabetes mellitus
97	6.3	15.0	Tuberculous pleurisy; osteo-arthritis
98	6.2	16.7	Cerebral hemorrhage
99	6.1	15.8	Influenzal pneumonia
100	6.1	16.7	Arteriosclerosis; myocarditis
	6.1		
101	6.1	30.0	Chronic glomerular nephritis
102	6.1	15.8	Gastric ulcer
103	6.1	27.2	Rheumatic fever
104	6.1	13.7	Parturition
105	6.0		Chronic glomerular nephritis
106	5.8		Epidemic meningitis
107	5.8	15.8	Infective cholangitis
108	5.8		Chronic glomerular nephritis; uremia
	5.2	60.0	
109	5.8	16.7	Undetermined
110	5.8	37.5	Multiple abscesses of kidney; chronic cholecystitis
111	5.8	17.6	Encephalitis; hypertrophied prostate
112	5.8	15.0	Lobar pneumonia
113	5.8	16.7	Traumatism to kidney
114	5.8	17.6	Acute cholecystitis
115	5.6	15.0	Hypertrophic cirrhosis
116	5.4	15.8	Diabetes mellitus
117	5.4		Subacute bacterial endocarditis
118	5.3	15.8	Aortitis and myocarditis
119	5.0	15.0	Lobar pneumonia
120	4.0		Diabetes mellitus

leukemia studied by Sandiford, Boothby and Giffin,[4] the amino-acid nitrogen blood values ranged from 5 to 16 mg. per hundred cubic centimeters, with an average of 10 mg.

Desqueyroux,[5] in 1923, studied the amino-acids and other nitrogen products in the blood of forty patients and three healthy persons, and he obtained increased values for the amino-acid nitrogen of blood in diabetes mellitus, nephritis with nitrogen retention, myocardial insufficiency and pneumonia. In pathologic conditions of the liver, irregular readings were obtained. On the contrary, Green, Sandiford and Ross,[6] in 1924, made 458 observations covering twenty pathologic conditions, and they found that the amino-acid nitrogen in the blood is maintained within normal limits with remarkable constancy and that such disease as uremia, diabetes, exophthalmic goiter and hepatic insufficiency furnish no exception to the rule.

In our study, the specimens of blood were drawn before breakfast, and the amino-acid nitrogen was determined according to Folin's [7] colorimetric method; the urea nitrogen determinations were made by Folin's [8] urease colorimetric method.

TABLE 2.—*Amino-Acid Nitrogen in Blood in Conditions Reputed to be Associated with Hyperamino-Acidemia*

Diagnosis	No. of Cases	Amino-Acid Nitrogen in Whole Blood, Mg. per 100 C.c.		
		Minimum	Maximum	Average
Diabetes mellitus	20	4.0	10.0	6.7
Chronic glomerular nephritis	5	5.5	8.2	6.5
Uremia	4	5.5	8.9	7.3
Hepatic cirrhosis	3	5.6	6.6	6.2
Normal	3	6.6	8.0	7.5

NOTE:—Where more than one determination was made, the average of all the readings in that case was taken.

In Table 1 we have enumerated in order, according to the amino-acid nitrogen values, our findings as to this substance and urea nitrogen in the blood of a group of 120 patients, representing a total of 160 examinations.

Assuming 8.5 mg. per hundred cubic centimeters to represent an abnormal level for the amino-acid nitrogen of blood, a perusal of Table 1 will show that the first twelve cases exhibited excessive values

4. Sandiford, K.; Boothby, W. M., and Giffin, H. Z.: The Amino-Acid Nitrogen in the Blood and Its Possible Relations to the Elevation of the Metabolism in Myelogenous Leukemia, J. Biol. Chem. **55**:23, 1923.

5. Desqueyroux, J.: Recherches cliniques sur l'amino-acidémie, Ann. de méd. **13**:20 (Jan.) 1923.

6. Green, C. H.; Sandiford, K., and Ross, H.: The Amino-Acid Content of the Blood in Normal and Pathologic Conditions, J. Biol. Chem. **58**:845 (Jan.) 1924.

7. Folin, O.: Laboratory Manual of Biological Chemistry, 1922, p. 259.

8. Folin, O.: Laboratory Manual of Biological Chemistry, 1922, p. 239.

for this substance. From a study of this table, it at once becomes apparent that no special conditions within this series were consistently associated with hyperamino-acidemia.

In Table 2 are enumerated the disease conditions to which high values of amino-acid in blood have been attributed, together with our findings in these same conditions.

In our series, consistently high readings were not found in diabetes mellitus, chronic glomerular nephritis, uremia or cirrhosis of the liver. An occasional high reading was obtained, but, in many instances, subsequent examinations gave normal figures. No attempt is made to interpret the individual high readings in the light of the diagnosis; on the contrary, our findings have failed to show a consistent association between hyperamino-acidemia and any pathologic condition.

In one instance, parallel observations were made on the blood of an eclamptic mother and that of a stillborn infant, the latter specimen being taken from the placental end of the umbilical cord very shortly

TABLE 3.—*Comparative Figures for Urea Nitrogen and Amino-Acid Nitrogen in Sixteen Specimens with Urea Nitrogen Values Exceeding 25 mg. per 100 c.c.*

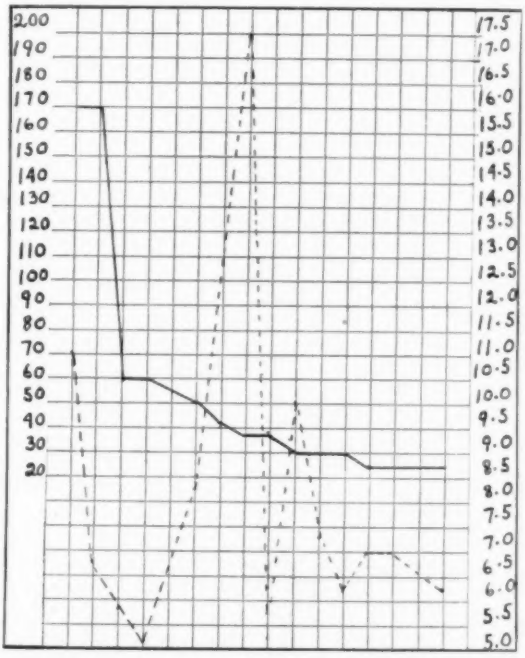
Mg. per 100 C.c. of Blood		Mg. per 100 C.c. of Blood	
Urea Nitrogen	Amino-Acid Nitrogen	Urea Nitrogen	Amino-Acid Nitrogen
171.2	11.0	37.5	5.8
171.2	6.8	30.0	10.0
60.0	5.8	30.0	7.4
60.0	5.2	30.0	6.1
55.0	6.6	27.2	7.0
50.0	8.2	27.2	7.0
42.8	12.0	27.2	6.6
37.5	17.5	27.2	6.1

after the death of the fetus. The fetal blood had an amino-acid nitrogen value almost twice that of the mother, rating 12 mg. per hundred cubic centimeters as against 6.6 mg. Higher values for amino-acids in the blood of the new-born infant appear to be the rule. In eighteen comparisons made by Morse,[9] in 1917, the reading was higher in the fetal blood in thirteen instances, lower in one, and identical readings were obtained in four cases.

Having in mind a possible relationship between retention of urea nitrogen and high amino-acid figures in the blood, we have grouped in Table 3 all of those cases which showed a reading in excess of 25 mg. of urea nitrogen per hundred cubic centimeters, and have concurrently tabulated the amino-acid figures. A study of these results shows that, while in an individual instance urea retention is apt to be accompanied

9. Morse, A.: The Amino-Acid Nitrogen of the Blood in Cases of Normal and Complicated Pregnancy and Also in the New-Born Infant, Bull. Johns Hopkins Hosp. **28**:199 (June) 1917.

by hyperamino-acidemia, this association is just as often completely lacking. As graphically represented in the chart, there was a marked absence of parallelism between the respective levels of urea nitrogen and of amino-acids in blood. Even when an abnormally high reading for amino-acids is obtained, it is not constant. Thus, in Case 5 (Table 1), the values of urea nitrogen and amino-acid nitrogen per hundred cubic centimeters of blood were 171.2 mg. and 11 mg. respectively; a subse-



Concurrent readings of the amino-acid nitrogen of blood in sixteen cases in which the urea nitrogen readings were in excess of 25 mg. per hundred cubic centimeters, showing the lack of parallelism between the values for the two substances. The left hand figures refer to the urea nitrogen values in terms of milligrams per hundred cubic centimeters and the solid line gives the respective values for this substance in the cases cited. The right hand figures refer to the amino-acid nitrogen values in terms of milligrams per hundred cubic centimeters, and the interrupted line gives the respective values for this substance in the same cases.

quent examination yielded the same reading for urea, but the amino-acid nitrogen had dropped to 6.8 mg.

Our findings in this respect are in accord with those of Green, Sandiford and Ross,[6] who found no apparent correlation between the

amino-acids and the degree of renal insufficiency or urea retention. Experimentally, Haden and Orr,[10] in 1923, produced intestinal obstruction in dogs, but although there was a marked increase in the blood urea, no change occurred in the amino-acid nitrogen content of the blood.

In Table 4 there are tabulated four comparative amino-acid readings between the blood and some other fluid.

TABLE 4.—*Comparative Readings of Amino-Acid Nitrogen in Blood and in Other Fluids*

Fluid: Mg. per 100 C.c.		Blood: Mg. per 100 C.c.	Diagnosis
Bile	14.6	6.6	Cerebral arteriosclerosis
Spinal fluid	4.6	10.0	Diabetic coma
Lung fluid	8.1	10.0	Diabetic coma
Chest fluid	5.6	7.0	Myocardial insufficiency

SUMMARY

An analysis of 160 amino-acid nitrogen determinations in blood on 120 patients failed to indicate any pathologic conditions with which abnormally high values for this element are consistently associated. In the twelve patients whose bloods gave readings in excess of 8.5 mg. per hundred cubic centimeters, no causal relationship between the malady and the hyperamino-acidemia was apparent. Furthermore, a study of twenty cases of diabetes mellitus, five of chronic glomerular nephritis, four of uremia, and three of hepatic cirrhosis, showed the average amino-acid nitrogen value in blood to be normal in all of these conditions, although individual instances of increased readings occurred in the first three groups. Abnormally high values frequently returned to normal in subsequent examinations. In a group of sixteen tests in which the urea nitrogen value of the blood exceeded 25 mg. per hundred cubic centimeters, there was concurrent elevation of the amino-acids in only four instances, and even then there was no parallelism between the two substances. No cases of leukemia or of acute yellow atrophy of the liver were included within this study.

616 Carlton Avenue.

10. Haden, R. L., and Orr, T. G.: Chemical Changes in the Blood of the Dog After Intestinal Obstruction, J. Exper. Med. **37**:365 (March) 1923; Chemical Changes in the Blood of the Dog After Pyloric Obstruction, J. Exper. Med. **37**:377 (March) 1923.

STUDIES ON ACUTE INTESTINAL OBSTRUCTION

II. ACUTE STRANGULATION *

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In the preceding paper [1] we have shown that acute intestinal obstruction may be divided both clinically and experimentally into acute simple obstruction and acute strangulation; that the symptomatology, length of life and lethal factors are different in each case. In uncomplicated simple obstruction death is probably due to starvation and its sequelae.

In this paper we report a series of experiments demonstrating that the foregoing factors in simple obstruction play little or no part in acute strangulation but instead that death is due to shock and toxemia. The rapidity with which these factors act varies with the length of intestine involved, the degree of arterial and venous obstruction and the location of the lesion.

No attempt will be made to review the extensive literature on the subject of intestinal obstruction. Only those articles which have dealt with experimentally produced strangulation will be briefly summarized. Von Albeck [2] was the first to produce experimental strangulation. He used loops from 6 to 8 inches (from 15 to 20 cm.) in length. His dogs died in collapse in from twenty-four to forty-eight hours, showing vomiting, diarrhea, subnormal temperature and spasms prior to death. He concluded death was due to the absorption of putrefactive toxins formed in the strangulated loop.

Eisberg [3] also produced strangulation but under morphin ether anesthesia. In his animals the minimum length of life was from three to seven hours, the maximum duration forty-two hours. His statements are rather indefinite and not detailed. In speaking of the cause of death he says: "Surely at times a devitalized segment appears to be responsible for a lethel outcome, long before there has been time for bacterial action to play a part in the results."

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1. Hausler, R. W., and Foster, W. C.: Studies in Acute Intestinal Obstruction. I. Different Types of Obstruction Produced under Local Anesthesia. Arch. Int. Med. **34**:97 (July) 1924.
2. Von Albeck: Arch. f. klin. Chir. **65**:569, 1902.
3. Eisberg, H. B.: Ann. Surg. **74**:584 (Nov.) 1921.

Murphy and Vincent [4] are the only other authors who have paid any particular attention to circulatory conditions in obstruction. Their work was on cats. Strangulation, venous obstruction and anemia were produced under ether anesthesia. Blood pressure tracings under ether anesthesia were taken by them on the carotid artery at irregular intervals. Such procedures have many disadvantages and introduce other factors, especially in a very sick animal. To quote them further, "the animals after from four to six hours were in such poor condition that it was difficult to etherize them and obtain a second reading, since the slightest excess of ether was fatal, and the low blood pressure tended to the formation of a clot in the cannula." The local anesthesia method used on the femoral artery in our series permits of hourly tracings with no inconvenience to the dog, and excludes vagal and sympathetic stimulation and ether intoxication. Murphy and Vincent report that with venous obstruction the height of intoxication was reached in from four to six hours. They believe the symptoms and death to be due to "bacterial endotoxemia."

MATERIAL AND METHODS

The operative detail has been given in a previous paper. All operations were performed on dogs under local anesthesia with careful aseptic technic. Definite lengths of bowel were twisted and tied with rubber tubing in such a way as to cause a complete venous obstruction. Temperature, pulse, respiration and blood pressure were taken before and at definite intervals after operation. Blood chemistry estimations were made in the chemical laboratory. All solutions were adequately checked. The following methods were used: Blood sugar: Haskins-Holbrook [5] modification of Shafer titration method, total nitrogen, Microkjeldahl, urea nitrogen, Microkjeldahl, chlorids, Folin.[6]

The dogs were kept under almost continuous observation from the beginning of the experiment until death. Necropsies were performed immediately. The abdominal organs were fixed and sectioned for microscopic examination.

EXPERIMENTAL OBSERVATIONS

From the first series of twelve dogs with acute strangulation the following five typical protocols illustrate the postobstructive course when different lengths of the intestine are involved.

4. Murphy and Vincent: Boston M. & S. J. **165**:684, 1911.
5. Haskins, H. D., and Holbrook, W. P.: J. Lab. & Clin. Med. **8**:747 (Aug.) 1923.
6. Folin, O. K.: Lab. Manual of Bio. Chem. Ed. 2, 1919.

PROCOTOL OF EXPERIMENTS

EXPERIMENT 1.—Dog 50, adult, tan terrier, male, weight, 23 pounds (10 kg.). Five inch (12.7 cm.) segment. Death in twenty-nine hours.

10:05 a. m. Temperature (rectal), 102.4 F.; pulse, 84; respirations, 20; blood pressure, 150 systolic.

10:15, operation. Five inches (12.7 cm.) of jejunum and ileum strangulated. Off table 10:30. Ran about the room.

12:00 noon. Temperature, 101.8; pulse, 110; respirations, 24; blood pressure, 146 systolic. Animal in good condition. Drank and vomited at frequent intervals.

2:00 p. m. Temperature, 98; pulse, 130; respirations, 28; blood pressure, 144 systolic. Whined frequently and seemed distressed.

5:00 p. m. Temperature, 99.2; pulse, 130; respirations, 28; blood pressure, 140 systolic. Howled frequently and was very nervous.

7:30 a. m. Next day. Temperature, 104.4; pulse, 190; respirations, 36; blood pressure, 110 systolic; the dog appeared to be very toxic and vomited frequently.

10:30 a. m. Temperature, 104.6; pulse, 190; respirations, 34; blood pressure, 90 systolic. Hardly able to walk.

2:00 p. m. Temperature, 105.6; pulse, 210; respirations, 68; blood pressure, 50 systolic. Dog moribund.

3:15 p. m., the dog was killed, and there was an immediate necropsy. Findings: Lungs, liver, spleen and kidneys were grossly normal. Peritoneal cavity contained considerable foul smelling fluid. Strangulated segment was ruptured, purplish black in color and necrotic. Generalized peritonitis.

EXPERIMENT 2.—Dog 53, brown female, weight, 30 pounds (13.6 kg.). Twelve inch (30 cm.) segment. Death in twenty-five hours.

4:15 p. m. Temperature, 101.4; pulse, 84; respirations, 18; blood pressure, 145 systolic.

4:30 p. m. Operation. Strangulation of 12 inches (30 cm.), upper ileum. Off table at 4:50. Walked to cage; few minutes later vomited.

9:00 a. m. Following day. Temperature, 101.6; pulse, 152; respirations, 26; blood pressure, 130 systolic. The animal looked sick. Frequent vomiting after drinking. Gait steady.

11:00 a. m. Temperature, 101.6; pulse, 164; respirations, 28.

12:00 noon. Temperature, 102.4; pulse, 200; respirations, 27; blood pressure, 120 systolic. The dog appeared much weaker.

1:30 p. m. Temperature, 103; pulse, 220; respirations, 32. The animal was still able to walk.

2:40 p. m. Temperature, 102.4; pulse, 210; respirations, 36; blood pressure, 98. Much weaker.

3:45 p. m. Temperature, 104.4; pulse, 210; respirations, 48; blood pressure, 80. Dog lay in the cage, unable to stand.

4:45 p. m. Temperature, 105.8; pulse, 280; respirations, 70; blood pressure, 50 systolic.

5:20 p. m. Dead. Immediate necropsy. Findings: Peritoneal cavity contained about 300 c.c. of dark, bloody, foul smelling fluid; the strangulated loop was ruptured. Other viscera were grossly normal.

EXPERIMENT 3.—Dog 56, adult female collie, weight, 28 pounds (12.7 kg.). Fifteen inch (37 cm.) segment. Death in twenty-two hours.

10:45 a. m. Temperature, 102.8; pulse, 72; respirations, 18; blood pressure, 160 systolic.

11:00 a. m. Operation. Fifteen inches (37 cm.) of lower ileum strangulalated. Off table at 11:20. Ran about room.

2:30 p. m. Temperature, 105.6; pulse, 74; respirations, 72; blood pressure, 152 systolic. There was marked thirst and frequent vomiting during the last two hours.

5:00 p. m. Temperature, 104.4; pulse, 84; respirations, 42; blood pressure, 145 systolic.

9:00 p. m. Temperature, 104.6; pulse, 160; respirations, 24; blood pressure, 124 systolic. Dog looked dejected; marked thirst and much vomiting.

8:00 a. m. Following day. Temperature, 107; pulse, 240; respirations, 56; blood pressure, 74 systolic.

9:00 a. m. Dead. Necropsy at once. Necropsy findings: Gangrenous, strangulated loop ruptured; belly full of bloody exudate, tissue very friable. Generalized peritonitis. Other viscera were grossly normal.

Experiment 4.—Dog 35, white bull, male, weight, 22 pounds (10 kg.). Eighteen inch (45 cm.) segment. Death in ten hours.

8:30 a. m. Temperature, 101.8; pulse, 94; respirations, 18; blood pressure, 152 systolic; white blood count, 6,900.

9:15 a. m. Operation. Eighteen inches (4.5 cm.) of upper ileum strangulated. Off table at 9:35. Ran around room. Whined, drank and vomited a few minutes later.

9:50 a. m. Temperature, 101.6; pulse, 160; respirations, 20; blood pressure, 150 systolic.

10:40 a. m. Temperature, 101.6; pulse, 162; respirations, 20; blood pressure, 118 systolic. Vomited frequently, very thirsty.

12:00 noon. Temperature, 99.1; pulse, 160; respirations, 22. Dog very listless. Vomited blood-stained bowel contents.

2:20 p. m. Temperature, 101; pulse, 180; respirations, 21; blood pressure, 102 systolic. Animal markedly shocked. Still able to walk; staggering gait.

4:20 p. m. Temperature, 101.2; pulse, 180; respirations, 22; blood pressure, 88 systolic. Hardly able to walk, fell frequently. Respirations irregular and loud. Drank occasionally and retched.

5:05 p. m. Temperature, 99.6; pulse, 180; respirations 26; blood pressure, 71 systolic. Advanced stage of shock.

7:06 p. m. Temperature, 99.6; pulse, 178; respirations, 26; blood pressure, 62 systolic; white blood cells, 10,700. No response to sensory stimuli.

8:05 p. m. Dead. Necropsy immediately. Findings: Lungs, liver, spleen and kidneys were grossly normal. Strangulated segment enormously distended, glistening black in color; contained 150 c.c. of dark bloody fluid, only slight odor. Stomach, duodenum and large intestine very anemic. Forty cubic centimeters of blood stained fluid in the peritoneal cavity.

Experiment 5.—Dog 36, adult Airedale male, weight, 30 pounds (13.6 kg.). Twenty-four inch (60.96 cm.) segment. Dead in seven hours.

10:30 a. m. Temperature, 102.2; pulse, 84; respirations, 16; blood pressure, 138 systolic; white blood count, 14,500.

11:30 a. m. Operation. Twenty-four inches (60.96 cm.) of lower ileum strangulated. Off table at 11:42. Ran about room, appeared normal.

11:50 a. m. Temperature, 102.6; pulse, 100; respirations, 26. Very thirsty, drank, vomited in a few minutes.

1:00 p. m. Temperature, 101.5; pulse, 170; respirations, 26; blood pressure, 120 systolic. Stuporous and dazed.

3:00 p. m. Temperature, 101.4; pulse, 180; respirations 36; blood pressure, 88 systolic. Dog weaker, when forced to get up staggered and leaned against cage for support. Respirations rapid and stertorous.

3:40 p. m. Temperature, 101.4; pulse, 182; respirations, 42; blood pressure, 44 systolic. Gradually getting weaker.

4:50 p. m. Temperature, 101.4; pulse, 220; respirations, 46; blood pressure, 42 systolic. Profound shock.

6:00 p. m. Temperature, 100.2; pulse, 228; respirations, 46; blood pressure, 42 systolic; white blood count, 18,400.

6:30 p. m. Dead. Necropsy findings: Abdominal and thoracic viscera grossly negative. Strangulated visceral segment distended, gangrenous, con-

tained 35 c.c. of dark, bloody fluid. Fifty cubic centimeters of similar fluid were found in the peritoneal cavity. No perforation.

Table 1 shows that there is a direct relationship between the length of bowel strangulated and the rapidity with which death ensues.

Naturally slight variations occur, due to the size and the type of the dog and the degree of venous occlusion produced at operation. However, the results definitely indicate that the longer the segment, the more pronounced the shock and the earlier the death. With the short segments, 12 inches (30 cm.) or less, shock although present, is not sufficient to cause a pronounced derangement and disorganization of the cardiovascular mechanism. The fall in blood pressure is only moderate, the pulse rate is not extremely rapid and the animals are able to overcome this primary phase, only to succumb later to a terrific toxemia and peritonitis. In the cases with long segments, 18 inches (45 cm.) or more, shock appears very early and is extremely severe. The blood

TABLE 1.—*Relationship Between Length of Bowel Strangulated and Death*

Dog No.	Weight in Pounds	Inches of Bowel Strangulated	Length of Life, Hours
50	23	5	29
60	42	6	28
53	30	12	25
37	26	12	24
34	17	12	23.5
56	28	15	22
40	35	15	20
31	50	18	12
35	22	18	10
32	47	24	9
36	30	24	7
39	35	26	8.5

pressure falls rapidly, the pulse rate climbs to a very high level and the temperature falls. The animal goes into collapse and dies from shock before toxemia can develop.

TOTAL ANEMIA

In this group, segments of bowel from 12 to 20 inches (from 30 to 50 cm.) in length were used. Three of the loops were found perforated at necropsy. This group does not parallel any clinical entities, but serves as a check on other observers' experiments. The following typical protocol well represents this series, of four dogs, in which the intestine was tied so tightly that a complete and instantaneous anemia was produced.

EXPERIMENT 7.—Dog 38, adult mongrel male, weight, 35 pounds (15 kg.). Twenty inch (50 cm.) segment. Dead in twenty hours.

10:30 a. m. Temperature, 102.8; pulse, 90; respirations, 16; blood pressure, 146 systolic; white blood count, 8,900.

11:00 a. m. Operation. Total anemia of 20 inches (50 cm.) of upper ileum. Off table at 11:20. Dog vomited two minutes after leaving the table.

12:00 noon. Temperature, 102.8; pulse, 140; respirations, 20; white blood count, 11,600. The animal vomited frequently and appeared distressed. Blood pressure, 134 systolic.

2:30 p. m. Temperature, 101.3; respirations, 28; pulse, 140; blood pressure, 125 systolic. Frequent vomiting. Gait steady, condition fair.

7:00 p. m. Temperature, 102.9; pulse, 140; respirations, 36; blood pressure, 115 systolic; white blood count, 10,500. Condition somewhat weaker but presented none of the marked shock symptoms seen in the previous series. No further observations were made during the night.

7:00 a. m. Temperature, 98.6; pulse, 240; respirations, 40; blood pressure, 38 systolic. Dog moribund.

7:35 a. m. Dead. Immediate necropsy. Findings: Lungs, spleen, kidneys and liver grossly normal. Peritoneal cavity contained small amount of blood stained fluid. Strangulated segment was slightly distended with gas. Pale, yellowish, pasty substance in the bowel lumen. Tissue of segment very friable, of a yellowish color, showed no perforation.

In this group it is obvious that the pathologic and the clinical pictures are entirely different from those of venous obstruction. The total anemia intestine shows little or no dilatation and contains no fluid. On the other hand, with venous obstruction the strangulated loop is dilated to two or three times its normal size and enormously distends the abdominal cavity. Furthermore, this group, in which there is no blood or fluid loss and only slight distention of intestine, does not show the acute collapse symptoms of the venous obstruction series. Instead, we have only a slight, gradual rise in pulse rate and a practically normal blood pressure during the first fifteen hours. Vomiting is less profuse, thirst slight, and the animal is much stronger. The temperature and respirations, however, show extreme elevation, which are not seen in the strangulation animals. The respiratory rate always rises in a few hours to 40 or 50 per minute, and in one case it averaged 120 per minute for over sixteen hours. The temperature shows a gradual continuous rise to an average maximum of 105 during the last five to eight hours.

The above experiments prove (1) that in acute strangulation blood loss and loop distention are important factors in the production of shock; (2) that a rapid rise in respiration and temperature, along with only slight variations in pulse rate and blood pressure, are indicative of toxemia and peritonitis.

RUBBER BAG SERIES

In order to show the relative importance of toxemia and shock in acute strangulation, five dogs were treated as follows. At operation the bowel segments were introduced into thin rubber bags, and a rubber catheter was tied around the base sufficiently tight to cause complete venous obstruction. This procedure prevents the absorption of toxins from the strangulated segment by the peritoneal serosa, without interfering with the distention of the segment by blood and gas.

EXPERIMENT 8.—Dog 12, black and white mongrel, male, weight, 31 pounds (14 kg.). Twenty-four inch (60 cm.) segment. Dead in eight and one-half hours.

9:00 a. m. Temperature, 102.6; respirations, 20; blood pressure, 145 systolic; white blood count, 14,200.

9:30 a. m. Operation. Twenty-four inches (60 cm.) of upper ileum and jejunum strangulated in rubber sac. Off table in twenty minutes. Drank freely, vomited.

10:00 a. m. Temperature, 102.6; pulse, 95; respirations, 24; blood pressure, 145 systolic.

11:00 a. m. Temperature, 102.6; pulse, 200; respirations, 30. Dog drank, retched and vomited frequently and appeared weaker.

12:00 noon. Temperature, 102.6; pulse, 240; respirations, 36; white blood count, 20,600. Frequent whining and vomiting.

1:05 p. m. Temperature, 102.8; pulse, 240; respirations, 50; blood pressure, 86 systolic. Animal rapidly going into shock, leaned heavily against cage.

2:30 p. m. Temperature, 102.3; pulse, 250; respirations, 42; blood pressure, 68 systolic. Dog very weak, in collapse.

3:30 p. m. Temperature, 104.3; pulse, 250; respirations, 48; blood pressure, 68 systolic; white blood count, 9,200.

4:45 p. m. Temperature, 104.6; pulse, 250; respirations, 52; blood pressure, 62 systolic. Could hardly walk. When aroused dog stood up and then fell.

5:30 p. m. Temperature, 104.6; pulse, 260; respirations, 48; blood pressure, 40 systolic. Moribund.

6:08 p. m. Dead. Immediate necropsy. Findings: Peritoneum normal, small amount of fluid present. No perforation. Intestine was greatly distended with gas and contained 250 c.c. of dark, bloody fluid. Gallbladder contained 20 c.c. concentrated fluid. Proximal intestine empty and anemic, of mottled appearance.

EXPERIMENT 9.—Dog 13, adult mongrel, male, weight, 30 pounds (13 kg.). Ten inch (25 cm.) segment. Death in Sixty-six hours.

March 9, 2:00 p. m. Temperature, 102.8; pulse, 86; respirations, 20; blood pressure, 150 systolic.

2:30 p. m. Operation. Ten inches (25 cm.) of jejunum strangulated in rubber sac. Off table in twenty minutes.

5:00 p. m. Temperature, 102.8; pulse, 110; respirations, 24; blood pressure, 145 systolic. Occasional vomiting. Condition good.

March 10, 8:00 a. m. Temperature, 102.6; pulse, 96; respirations, 26. Dog appeared in excellent condition; wagged tail, walked about with no difficulty. Respirations were slightly labored.

2:00 p. m. Frequent vomiting, appeared weaker.

March 11, 8:30 a. m. Temperature, 103.2; pulse, 108; respirations, 26. Animal in good condition.

5:00 p. m. Temperature, 104; pulse, 130; respirations, 28; blood pressure, 138 systolic. Dog looked toxic.

March 12, 8:00 a. m. Dog moribund. Killed. Necropsy findings: Sac distended with gas and contained about 100 c.c. bloody fluid. Perforation just proximal to tie. Generalized peritonitis.

In the foregoing experiments long and short loops were used. From the previous experiments it was evident that shock was the predominating lethal factor when long segments were used. Thus the use of the rubber bag to prevent any possible absorption should not materially effect the duration of life. A comparison of Experiment 4 (segment 24 inches, death in seven hours) with Experiment 8 (segment 24 inches placed in rubber sac, death in eight and one-half hours) shows that

the change in temperature, pulse, respiration, blood pressure and duration of life are practically identical in each case. It is thus evident that toxemia is only of minor importance, since the prevention of the absorption of toxin does not materially affect the outcome. With short loops, however, where toxemia is more predominant and shock of a milder degree, the length of life should be markedly affected. A comparison of Experiment 2 (segment 12 inches, death in twenty-five hours) with Experiment 9 (segment 10 inches, in rubber bag, death in sixty-six hours) reveals this difference in a very striking manner. The foregoing experiments prove the following: (1) In the rapidly fatal cases of long segment strangulation toxemia is not an important lethal factor; (2) in the short segments toxemia is very pronounced.

RELEASE OF STRANGULATION

To show the effect of release of the strangulation after shock symptoms had become moderately advanced experiments of the following nature were performed.

EXPERIMENT 14.—Dog 47, adult brown male, weight, 50 pounds (22 kg.).

11:00 a. m. Temperature, 101.2; pulse, 62; respirations, 16; blood pressure, 146 systolic.

11:45 a. m. Operation. Strangulation of 20 inches (50 cm.) of upper ileum. Off table in fifteen minutes. Vomited slight amount of blood tinged mucus. Voided 175 c.c. urine. Small stool.

12:45 p. m. Temperature, 97; pulse, 50; respirations, 28; blood pressure, 132 systolic. Dog appeared to be very sick. Whined continuously, seemed cold. Heater placed in cage.

2:00 p. m. Temperature, 104.7; pulse, 206; respirations, 30; blood pressure, 100 systolic. Condition worse.

2:55 p. m. Temperature, 105; pulse, 184; irregular, respirations, 32; blood pressure, 78 systolic. Anal sphincter relaxed.

4:00 p. m. Temperature, 106; pulse, 170; respirations, 42; blood pressure, 75 systolic. Appeared deeply shocked, hardly able to stand.

4:20 p. m. Belly opened under local anesthesia, strangulation relieved. Gut appeared very black, apparently not viable, but returned to belly cavity without resection.

5:45 p. m. Temperature, 106; pulse, 172; respirations, 40; blood pressure, 84 systolic. Passed small liquid stool twenty minutes after removal of strangulation. Given one grain morphin by hypodermic.

6:45 p. m. Temperature, 106.5; pulse, 170; respiration, 50; blood pressure, 90 systolic. Frequent small, fluid stools. Sleeping quietly.

7:30 p. m. Temperature, 105.2; pulse, 210; respiration, 50; blood pressure, 95 systolic. Five hundred c.c. of 5 per cent. glucose in physiologic sodium chlorid solution given subcutaneously. Condition much improved.

April 11, following day.

8:00 a. m. Temperature, 103.2; pulse, 100; respirations, 24; blood pressure, 115 systolic. Dog appeared to be in good condition.

From this time the recovery was uneventful.

This animal was sacrificed one week later. The segment previously strangulated was markedly thickened, hard and indurated and mottled purplish in color. Lumen patent but smaller than normal. Peritoneum smooth and glistening, with no signs of adhesions.

These experiments illustrate very clearly the degree of systemic depression produced by the violent peristalsis of the proximal segment and the stretching of both the parietal and visceral peritoneum by the strangulated intestine. These loops are always distended to about two or three times their former length and diameter, completely filling and distending the peritoneal cavity.

Before the release of the obstruction the animals were in a precarious condition. The blood pressure was low, the pulse rapid and feeble, respirations fast and stertorous, and muscular weakness was pronounced. The dogs were hardly able to stand, and paid little attention to external stimuli.

As soon as the obstruction is released a marked change occurs. The animal is visibly relieved, the depression passes, vomiting ceases and the bowels are emptied by two or three liquid stools. He is soon able to walk about and drinks large quantities of water. Soon the pulse becomes slower and of a better quality. The temperature returns to normal. The blood pressure and respirations show few changes during the first three hours. The following day the animal is in a good condition and usually makes an uneventful recovery. The loop fluid, which was always allowed to pass into the distal segment, produces a mild diarrhea, but apparently without any marked deleterious effect on the animal.

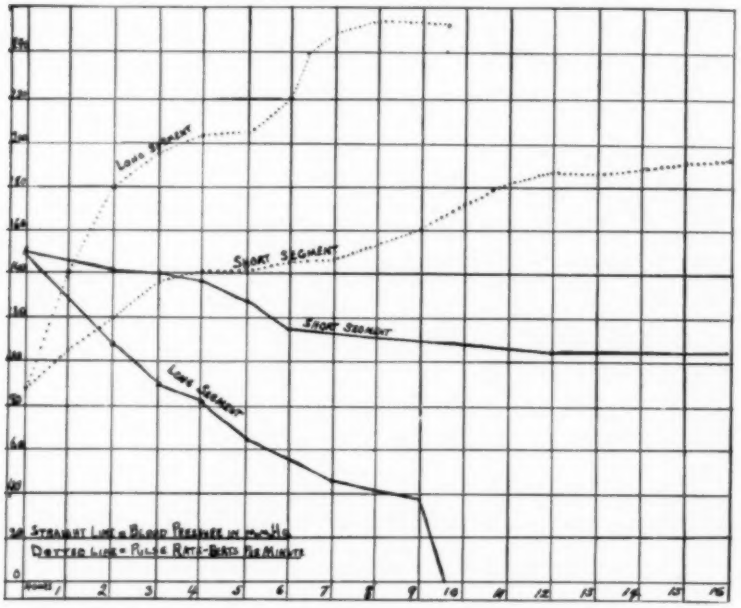
The foregoing results further indicate that shock is a predominating lethel factor in early strangulation. Toxemia apparently has not developed to any marked degree. Further discussion of these experiments will be given in a subsequent article on the treatment of acute intestinal obstruction.

OBSERVATIONS ON PULSE AND BLOOD PRESSURE

One of the most outstanding features of acute strangulation experimentally produced is a constant, pronounced fall in blood pressure, and a coincident and proportionate increase in pulse rate. These striking observations are graphically presented in the chart. A definite relation exists between the length of segment strangulated and the blood pressure and the pulse changes. In the long segments a rapid fall in blood pressure from an average of 150 mm. of mercury systolic to 90 mm. occurs within the first three hours. At the end of five hours it has dropped to 60 mm. and by seven hours has usually reached the 40 mm. level. At the same time the pulse rate jumps from an average of 80 to 90 per minute to about 140 at the end of the first hour, 180 or above at the end of two hours, 200 at four, and from there on until death it averages about 240 beats.

In short segments the blood pressure falls to approximately 110 mm. systolic in the first six hours and remains at about this level until

several hours before death. At this time a very rapid fall begins, often amounting to 60 mm. in an hour's time. The pulse rate usually shows a fairly rapid rise within the first six hours to an average of 140 per minute. After this level has been reached there is generally only a slight elevation during the next ten hours. After sixteen hours, however, a profound toxemia has developed and the pulse shows a rapid increase to over 200, at which level it continues until death.


LONG SEGMENT
SHORT SEGMENT
SHORT SEGMENT
LONG SEGMENT
STRAIGHT LINE = BLOOD PRESSURE IN MM. Hg.
DOTTED LINE = PULSE RATE-BEATS PER MINUTE
HOURS 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16

Composite curves of pulse and blood pressure variations in long and short segment strangulation.

TEMPERATURE

The temperature in acute strangulation is so subject to fluctuation that it does not give a reliable indication of the pathology or condition of the experimental animal. Some dogs with long strangulated segments, profound shock and early death show a temperature curve that does not vary over one-half a degree from the normal. Others, with exactly similar pathology, have a rapid fall of three or four degrees within the first two hours. In general, however, the longer segments show a slight fall at the end of two hours and then a more rapid progressive decline until death. The blood pressure and temperature curves are very similar in time and extent. In short segments there is

little or no variation within the first ten hours. After this time, however, a marked toxemia or peritonitis has developed, and the temperature is usually very high, averaging about 105 F.

The clinical value of external heat applications was well demonstrated in several cases of profound shock, a subnormal temperature of 97 F., rising in an hour's time to 103 F. with marked improvement in the animal's general condition.

RESPIRATION

In all cases of acute strangulation there was a definite increase in respiratory rate. The curve parallels that of the pulse rate very closely. In the long segment cases there is an early rise from a normal of approximately 20 to an average of 44 per minute. They usually become shallow and thoracic in type, and toward the last are very irregular. With the shorter segments there is an early increase of about ten respirations per minute, at which level it remains until the onset of profound toxemia, when a rapid elevation to 40 or more takes place.

TOXICITY OF LOOP AND PERITONEAL EXUDATES

Much work of a very technical nature has been done on the chemistry and toxicity of the loop fluid in dogs in which no circulatory disturbances were produced. The degree of toxicity was determined for the most part by intravenous injection of loop content, but since the normal bowel contains many proteoses and amins which are very toxic on intravenous injection, too much weight cannot be placed on the results of such experiments. There can be no question about the toxicity of body fluids and bowel content when these are mixed with bacteria and left in a virtual incubator for twelve hours or more. This is evidenced in the peritonitis following bowel rupture, in which cases death ensues in a relatively short time from a terrific toxemia.

The purpose in the following experiments was to determine the relative toxicity of the loop content of dogs dying in less than twelve hours, and to ascertain its relation to the sudden collapse beginning two or three hours after strangulation, to which certain authors refer as a profound toxemia.

In acute strangulation, obstruction of the venous and lymphatic channels is produced by the constricting band and the subsequent thrombosis of the mesenteric vessels. Thus the only possible path of absorption is by a transudation of the loop fluid through the strangulated bowel walls into the peritoneal cavity and thence by the peritoneal lymphatics into the blood stream. Further, the inflammatory reaction of the peritoneal serosa to this transudate may partially detoxicate it. Therefore, it seemed unphysiologic to inject this fluid intravenously,

and accordingly in the following experiments we have made all injections intraperitoneally. The fluid was drained from the strangulated segments immediately after death, filtered through sterile gauze to facilitate injection, and without further treatment, either by heat or chemicals, injected intraperitoneally. By this simple treatment any increase or decrease in toxicity by necropsy changes was prevented.

In the first experiment a mixture of the loop fluids of Dog 32, dying in nine hours, and Dog 31, dying in twelve hours, was injected into a normal, young dog, weighing 12 pounds (5.4 kg.), with the results seen in Table 2.

TABLE 2.—*Experiment 16, Dog 33, Young Mongrel, Male, Weight 12 Pounds (5.4 kg.).*

Time	Temperature	Respiration	Pulse	Amount of Fluid
6: 30 p. m.	103.0	16	90	Normal
6: 40 p. m.	103.0	16	90	20 c.c.
7: 30 p. m.	102.8	22	96	20 c.c.
8: 30 p. m.	102.4	28	110	20 c.c.
9: 00 p. m.	.....	..	...	20 c.c.
Next day				
8: 15 a. m.	104.0	34	180	No injection

The dog showed signs of peritonitis for a few days but made an uneventful recovery.

In order to test the toxicity of early loop fluid in massive doses the entire loop contents, 100 c.c., of a dog dying in seven hours (Experiment 5, Dog 36), was injected in one dose, with the result seen in Table 3. The fluid was left on ice over night.

TABLE 3.—*Experiment 17, Dog 38, Young, Black and White, Male Mongrel Weight 15 Pounds (6.8 kg.).*

Time	Temperature	Respiration	Pulse	Amount of Fluid
9: 30 a. m.	103.4	20	100	Normal
9: 45 a. m.	103.4	20	100	104 c.c.
1: 20 p. m.	103.3	28	134	
4: 00 p. m.	104.0	28	160	
Next day				
9: 00 a. m.	103.1	30	120	
11: 00 a. m.	103.2	26	118	

Half an hour after the injection the dog showed marked salivation, dry nose and restlessness, and vomited once. Two hours later he appeared depressed, but walked about quite normally. After six hours the condition was much improved. On the following day the dog was in good condition, and made an uneventful recovery. An exploratory laparotomy on this animal three weeks later revealed a normal peritoneal serosa.

In dogs dying from experimental strangulation there is always a bloody exudate found at necropsy in the abdominal cavity. The total quantity of this fluid was gathered from one dog (Dog 31, dying in

twelve hours), 60 c.c. in amount, and injected intraperitoneally with the results seen in Table 4.

About two hours after the injection the dog appeared slightly depressed. He held his belly rigid and the respirations were shallow and thoracic in type. The nose was dry and he drank freely. He passed one liquid stool. The following day the animal appeared entirely normal.

In the preceding experiments no attempts were made to kill the bacteria in the loop fluid before its injection into the experimental animal. Accordingly, part of the reaction obtained is undoubtedly due to the subsequent peritonitis following this massive bacterial injection. The fact that no severe peritonitis followed demonstrates the enormous ability of the peritoneum to overcome bacterial invasion. All of the injected animals were small and young, and therefore, if the fluid was very toxic, should have shown extreme reaction to these doses.

The process of transudation from the strangulated intestine and absorption via the peritoneal serosa is a gradual one, beginning soon

TABLE 4.—*Experiment 18, Dog 37, Brown, Mongrel, Male, Weight 11 Pounds (5.0 kg.).*

Time	Temperature	Respiration	Pulse	Amount of Fluid
10: 35 a. m.	103.2	22	120	Normal
10: 40 a. m.	.....	..	...	60 c.c.
11: 05 a. m.	103.4	22	110	
1: 30 p. m.	104.4	26	110	
3: 35 p. m.	103.5	28	80 Irreg.	
6: 00 p. m.	103.0	22	62	
Next day				
8: 00 a. m.	102.3	18	60	

after the strangulation is produced. The amount of this transudation varies at different times, according to the pressure within the strangulated loop and the force of the incoming arterial flow. In the first experiment, therefore, amounts similar to what might have been absorbed were given at hourly intervals. Since the reaction was very slight and no great degree of toxicity was evidenced in the first animal, the second animal was given the entire loop contents in one massive dose. This procedure gave a more pronounced reaction, but this animal likewise quickly recovered. The free peritoneal fluid, which is a mixture of transudate and peritoneal exudate, proved to be relatively nontoxic.

The preceding protocols show that the fluids which accumulate in the peritoneal cavity and strangulated loops of less than twelve hours' duration are not highly toxic when introduced intraperitoneally, even in massive doses. Furthermore, they indicate that the sudden and extreme collapse following long segment strangulation cannot be explained entirely as a profound toxemia.

BLOOD CHEMISTRY

Table 5 shows the changes in blood urea, nonprotein nitrogen, sugar and chlorids in five of the strangulation dogs.

It will be seen that there is an increased nonprotein nitrogen in all cases. The final determinations, however, are not far above the normal level. They probably indicate both urinary retention and increased tissue destruction. Urea nitrogen also consistently increases, but does not always parallel the nonprotein nitrogen curve. Blood sugar shows marked fluctuations, usually within normal limits; at no time was there a definite continuous hypoglycemia or hyperglycemia. In two dogs the sodium chlorid percentage is decreased slightly, in two a slight

TABLE 5.—*Blood Chemistry in Five Dogs*

		Blood Chemistry, Amounts per 100 C.c.				
Dog No.	Hours After Operation	Total Nonprotein Nitrogen, Mg.	Urea Nitrogen, Mg.	Sugar, Mg.	Sodium Chlorid, Mg.	Length of Life
36	0	28	9.6	114	501	7 hours
	7	50	22.4	66	501	
32	0	30	19.0	101	478	9 hours
	4	..	23.0	173		
	6	..	25.0	150	412	
	7	42	31.0	90		
	8	..	29.0	137		
	9	60	36.0	114	379	
35	0	32	9.8	98	462	10 hours
	6	..	....	129		
	10	42	18.3	85	501	
31	0	28	11.5	104	478	12 hours
	3	..	16.5	95		
	5	..	16.0	78		
	6	..	17.0	86	495	
	7	..	26.5	91		
	8	28	25.0	98		
	9	35	28.0	82		
	10	28	24.0	114	501	
37	0	22	12.0	81	500	24 hours
	6	24	14.0	92	470	
	12	30	19.0	67	445	

increase was noted, and in the other there was no change. The chlorid variations apparently have little significance.

Immediately after the strangulation is produced, violent peristalsis begins in the proximal segment and in five to fifteen minutes is followed by intense retching and vomiting. The character and frequency of vomiting and the type and amount of vomitus vary at different stages. At first it contains the typical stomach content, acid in reaction, not bile stained and composed largely of a watery fluid mixed with partially digested food. This primary vomiting gives only short relief and is soon followed by smaller amounts of bile-stained alkaline material, evidently the content of the bowel between the stomach and the point of obstruction.

After this initial cleansing of the proximal intestine has been completed the frequency of vomiting and the character and amount of vomitus depends entirely on the fluid intake. If the dogs are allowed to drink all of the water they desire, the vomiting is very frequent, from every ten to fifteen minutes, profuse in amount and consisting entirely of a clear, watery mucus, alkaline in reaction. At first sight it seems evident that the dogs are losing a large quantity of fluid by profuse intestinal secretion and this undoubtedly accounts for the prevalent belief that death in obstruction is due to dehydration. An accurate measurement of the fluid intake and the amount of vomitus shows, however, that the two are practically identical. Over 90 per cent. of the vomitus is ingested water and the remainder is thick, mucous intestinal secretion. Thus, with each attack of emesis the animal does not lose more than from 10 to 20 c.c. of fluid.

On the other hand, if the dogs are allowed no fluids by mouth the picture is greatly altered. The frequency of vomiting is markedly decreased, usually occurring only about once an hour. However, when the vomiting spells do come on they are much more severe, consisting almost entirely of a five to ten minute period of intense retching followed by the regurgitation of from 20 to 30 c.c. of a thick, tenacious, stringy mucus. This slimy material is the typical secretion of acute strangulation and it varies little, either in character or amount, from this point until death. Stercoraceous or fecal vomiting is never seen. This substantiates the belief that fecal vomiting never occurs in obstruction, but rather that the foul smelling fluid in low simple obstruction is due to the bacterial decomposition of the stagnant intestinal secretions accumulating in the proximal segment.

An analysis of this characteristic strangulation secretion, which begins within forty-five minutes after the obstruction is produced, reveals the following facts: Physically it is a clear, yellowish viscid fluid resembling egg albumin. Chemically it is mucin, a glycoprotein, secreted by the goblet cells of the intestinal mucosa. Titration tests for proteolytic and lypolytic enzyme action are practically always negative, thus indicating a complete absence of pancreatic juice and succus entericus. After the first vomitus of stomach contents the regurgitated fluid is always alkaline and gives a negative test for traces of free and combined hydrochloric acid. Gmelins' and Pettenkofers' tests for bile pigment are always negative. At necropsy the gallbladder is never distended and usually contains but little bile.

Kidney excretion shows a similar inhibition. Practically all dogs dying fifteen hours or less have an almost complete postobstructive anuria. Micturition does not occur and at necropsy the bladder is usually empty. The increase in blood urea and nonprotein nitrogen previously noted is evidently largely due to retention.

SUMMARY

The entire picture then reveals the following facts:

1. That in acute strangulation dehydration is an almost negligible factor, the total intestinal secretory loss being less than 200 or 300 c.c. Urinary secretion is almost nil.

2. There is no appreciable loss of bile, pancreatic, intestinal, or gastric juices, but rather there is a total inhibition of these secretions.

3. The absence of urine and the extreme fall in blood pressure indicate that the kidney and adrenals suffer in a like manner from this extreme systemic depression.

4. The absence of hydrochloric acid in the vomitus plus the relatively normal blood chlorids and the absence of alkalosis rules out of consideration hypochloremia as a lethal factor.

COMMENT

A careful clinical comparison of patients with simple obstruction and acute strangulation shows that the two processes are radically different. The former lives from three to eight days without food or water, dying eventually either of (1) inanition and dehydration, or (2) peritonitis following perforation. Collapse symptoms are not present until the last day. The course is a slow, gradually progressive one which terminates fatally, in toxemia or collapse. On the other hand, strangulation is an acute affair characterized by profound collapse and resulting in death usually in less than thirty-six hours. In a previous paper we have shown that experimentally and clinically this classification is justified.

Acute strangulation has been further subdivided into (1) long loop obstruction and (2) short loop obstruction. Clinically, the first group is represented by volvulus, and extensive internal strangulation, the second by strangulated inguineal, femoral and umbilical hernias and intussusception. We have shown that in both of these groups the course is so rapid that hypochloremia, alkalosis, dehydration and inanition do not have time to develop. It is thus evident that the usually assumed causes of death in simple obstruction play little or no part in acute strangulation.

With long loops the predominant lethal factor is shock. This is indicated by the early and extreme fall in blood pressure, fast thready pulse, rapid sighing respirations, marked thirst, subnormal temperature, and pronounced muscular weakness. The rapid recovery following the release of the strangulation and the slight toxicity of early loop fluid further verifies this statement. The factors producing this shock are as follows: (1) excruciating pain due to the constant stretching of the visceral and parietal peritoneum by violent peristalsis and abdominal

distention; (2) low blood pressure and its direct effects, namely, diminished rate and volume of blood flow, capillary stasis, decreased metabolism, glandular inactivity, etc.; (3) blood loss from hemorrhage into the bowel lumen.

If the loops are short, shock, although present, is not of sufficient intensity to cause death. The dogs withstand this primary systemic depression and thus sufficient time is allowed for toxemia and peritonitis to develop. The poisonous products responsible for the development of this toxemia are not formed in the intestine above the obstruction but are produced by bacterial decomposition within the strangulated loop.

In brief, then, death in acute intestinal strangulation is due to a varying combination of shock and toxemia. The preponderance of one or the other of these causes being largely determined by the length of bowel involved and the degree of venous occlusion.

A point of considerable clinical interest is the fact that an intestine segment when strangulated always stretches two or three times its former length. For example, a loop 12 inches (30 cm.) long at operation shows at necropsy a length of 30 inches (76 cm.) or more. It is thus evident that the measurements given in surgical reports of gangrenous bowel resection do not represent the actual length of intestine involved.

CONCLUSIONS

1. Dehydration, hypochloremia, alkalosis and inanition are not present to any appreciable degree in acute intestinal strangulation.

2. The blood chemistry estimations show a considerable increase in urea and nonprotein nitrogen. The other constituents remain practically normal.

3. The length of the strangulated segment determines the degree of shock, toxemia and the rapidity with which death ensues.

4. The loop fluid of long segment strangulation is relatively nontoxic when injected intraperitonally.

THE DETERMINATION OF PHENOLSULPHONEPHTHALEIN IN THE URINE IN JAUNDICE*

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The purpose of this communication is (1) to discuss the errors introduced during the colorimetric determination of phenolsulphonephthalein in the urine when the color of the dye is obscured by the bile pigments, and (2) to offer a method which permits of fairly accurate estimation of renal function, as expressed by the rate of excretion of phenolsulphonephthalein even though marked jaundice is present.

Rowntree and Geraghty [1] noted in their paper, in 1910, that urinary and biliary pigments may be removed from urine by basic lead acetate. No details of the use of this substance were discussed. In 1921 a method was reported by Burwell and Jones,[2] in which it was proposed that the use of a saturated alcoholic solution of zinc acetate precipitated both bile and blood pigments. The following paragraph is a quotation from the paper suggesting the use of zinc acetate.

> Phenolsulphonephthalein is injected in the usual manner, and the urine collected after the usual interval of two hours and ten minutes. This specimen is diluted up to 500 c.c. with tap water. To 20 c.c. of this diluted urine is added 20 c.c. of a saturated alcoholic solution of zinc acetate, which precipitates out bilirubin and hemoglobin. Filtration yields a clear solution, now free of bile pigments and hemoglobin. Twenty cubic centimeters of this clear filtrate is made alkaline with 5 c.c. of saturated sodium hydroxid solution to bring out the full color of the dye, and made up to 40 c.c. with tap water. This solution is clear and is read directly against a known standard of phenolsulphonephthalein. In order to correct for dilution, the percentage reading is multiplied by two.

In a preceding paragraph this statement is made: "This procedure permits practically 100 per cent. of phenolsulphonephthalein to remain in the filtrate." In the controls which were made by the authors who suggested the use of zinc acetate, no mention is made of the volume of jaundiced urine to which the estimated phenolsulphonephthalein had been added.

I. ERRORS INTRODUCED BY THE PRECIPITATION OF BILE PIGMENTS BY ALCOHOLIC ZINC ACETETE

When a known and constant quantity of phenolsulphonephthalein is added to increasing volumes of similar urine obtained by mixing

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1. Rowntree, L. G., and Geraghty, J. T.: J. Pharmacol. & Exper. Therap. **1**:579, 1909-1910.

2. Burwell, C. S., and Jones, C. M.: The Removal of Bile and Blood from the Urine, J. A. M. A. **77**:462 (Aug. 6) 1921.

numerous specimens from a deeply jaundiced patient, and the phenolsulphonephthalein determined by precipitation with zinc acetate following the methods described in the foregoing, two results have been obtained in the experiments of the author which do not agree with those reported previously.

One 0.5 c.c. of phenolsulphonephthalein was added to varying volumes of urine from a patient suffering from obstructive jaundice. Determination with Hynson, Dunning and Westcott standards checked with known concentrations of dye. Six milligrams of dye per cubic centimeter when diluted to 1 liter equals 100 per cent. Bile pigments were precipitated by the zinc acetate method.[2]

TABLE 1.—*Adsorption of Dye When Zinc Acetate Is Used*

Volume of Urine, C.c.	Phenolsulphonephthalein Added, per Cent.	Phenolsulphonephthalein Estimated, per Cent.	Phenolsulphonephthalein Loss, per Cent.	Color Comparison
50	50	50	0	Excellent
100	50	45	10	Good
150	50	40	20	Fair
200	50	35	30	Poor
250	50	30	40	Poor

In a series run with a specimen of urine obtained from a case of partial obstruction of the common duct, the average loss, when 250 c.c. of urine was used with varying quantities of phenolsulphonephthalein, was less than 25 per cent. and the colorimetric comparisons were good or fair throughout. The loss was negligible when similar experiments were done with normal urine. Comparing these figures with those in Table 1, it follows that with increasing concentration of bile pigment there is an increasing loss of phenolsulphonephthalein when the bile pigments are precipitated by alcoholic zinc acetate, and similarly the color comparison becomes less efficient. With urine containing less bile pigment, a better color comparison is obtained and there is less dye lost during precipitation. It should be noted that with the urine used in the experiments described in Table 1 the colorimetric comparison was poor when the urine volume was 200 c.c. Above this more or less critical volume for that specimen of urine, comparison was unsatisfactory. Similar results have been obtained with other concentrations of dye which are encountered in this test of renal function, the critical volume dependent, of course, on the concentration of bile pigment.

From the foregoing it is evident that the determination of phenolsulphonephthalein in the presence of jaundice by the precipitation of bile pigments by alcoholic zinc acetate may lead to uncertain results because of the variable loss of the dye during the process of precipitation. The dye is probably adsorbed by the zinc pigment precipitate.

II. THE ADSORPTION OF PHENOLSULPHONEPHTHALEIN INCIDENTAL TO THE USE OF BARIUM HYDROXID AS A REAGENT TO PRECIPITATE BILE AND URINARY PIGMENTS

Another substance, barium hydroxid, has been used by the author to remove bile and urinary pigments from the urine where it was desired to determine phenolsulphonephthalein.

Advantage was taken of the fact that bilirubin is believed to be an organic acid,[3] whose salts of the alkaline earth group of metals are insoluble in basic solutions. Barium,[4] one of that group, is particularly suitable, not only because it precipitates both bile and urinary pigments, but also because it forms a fairly concentrated solution of its hydroxid (about fifth molar), at ordinary temperatures. It is highly ionized, and hence there is available a high concentration of hydroxyl ion. From these properties it follows that if barium hydroxid is added in sufficient quantity to urine containing phenolsulphonephthalein, bile pigments and

TABLE 2.—*Adsorption of Dye When Barium Hydroxid Is Used*

Volume of Urine, C.c.	Phenolsulphonephthalein Added, per Cent.	Phenolsulphonephthalein Estimated, per Cent.	Phenolsulphonephthalein Loss, per Cent.	Color Comparison
50	50	45	10	Excellent
100	50	40	20	Good
150	50	36	28	Good
200	50	30	40	Fair
250	50	25	50	Poor

urinary pigments, the pigments will be precipitated and the color of the dye brought out. After dilution and filtration, suitable colorimetric comparison is possible under most circumstances.

It has been shown previously that there is a loss of phenolsulphonephthalein during the precipitation of zinc pigment compounds. Does adsorption of dye also occur when barium hydroxid is used?

Table 2 illustrates that adsorption does take place. The urine was from the same collected specimen used in the experiments of Table 1. The procedure was as follows: After addition of dye and barium hydroxid, the mixture was diluted to 1 liter and filtered. It has been found that the amount in cubic centimeters of saturated barium hydroxid necessary to produce good colorimetric comparisons is equal to the volume of urine plus 50 c.c.; that is, with 50 c.c. of urine, 100 c.c. of barium hydroxid is used; in the same way with 100 c.c. of urine, 150 c.c. of barium hydroxid, has given the best determinations. Dilu-

3. Mathews, A. P.: Physiological Chemistry, New York, William Wood & Co., 1916, p. 414-415.

4. Smith, A.: Inorganic Chemistry, New York, Century Company, 1915, p. 331, 612.

tion of a portion of the filtrate with its own volume permits of better comparison with the standard and serves as a check.

An excess of saturated barium hydroxid (equal to the volume of urine plus 50 c.c.) is added to the urine volumes noted in Table 2. The addition of phenolsulphonephthalein and its determination is as in Table 1. Dilution to 2 liters permits better color comparison and readings.

Table 2 is apt to be misleading. Barium hydroxid does not always give colorimetric comparisons better than zinc acetate. Quite often the reverse is true. It is almost invariably so, however, when the urine contains much bile pigment. Under these circumstances, in the hands of the author, better colorimetric comparisons are available, if an excess of barium hydroxid is used. Because of this and because of the simplicity of the technic (only one reagent beside the phenolsulphonephthalein is needed), the influence of barium hydroxid on urine containing bile pigments and phenolsulphonephthalein has been studied within the ranges of dye encountered in the performance of the phenolsulphonephthalein test. From the results, a fairly accurate method of determination of the dye in jaundice has been developed.

III. THE RELATIONS BETWEEN THE QUANTITY OF PHENOLSULPHONEPHTHALEIN PRESENT AND ITS ADSORPTION DURING BILE PIGMENT PRECIPITATION

In general, finely divided solids unite with substances in solution, so that if the solid be filtered off, the finely divided material previously in suspension contains more or less of the substance in solution. Adsorption [5] is the term generally used to describe this process of separation. There is somewhat of a direct relationship between the adsorbing surface and the adsorbed material. The amount adsorbed by charcoal, for example, at a given temperature is given by the expression $\frac{\frac{X}{m}}{C1/n} = K$ where X/m is the amount adsorbed per unit weight of charcoal, C is the equilibrium concentration of the substance in solution, and n and K are constants determined empirically. The curve of the reaction drawn by plotting the amount of chemical change (quantity adsorbed) against the equilibrium concentration is a parabola. The more dilute the solution the greater is the quantity adsorbed, and at these dilutions the curve of adsorption is for practical purposes a straight line. This is especially significant in the adsorption of phenolsulphonephthalein by the barium precipitate for: (1) the dilution is low, ranging from 0 mg. to 6 mg. (0 to 100 per cent.); (2) the range is so small that theoretically a

5. Bechold, H.: Die Kolloide in Biologie und Medizin, Dresden and Leipzig, Theodor Steinkopff, 1922, p. 21 et seq.

straight line of adsorption should be obtained with adsorption experiments over the concentration range of dye. If the adsorption curve is a straight line, then a method presents itself by which the error introduced by adsorption may be measured.

Table 3 shows some of the protocols of experiments performed to determine the relation between the concentration of the dye present and the quantity adsorbed. Barium hydroxid in excess was used on collective urines obtained from cases of jaundice of different severity.

The relation between dye added and subsequently adsorbed after addition of barium hydroxid. Within the limits of error of the experiments, for clinical purposes, the adsorption of phenolsulphonephthalein in the range studied is constant for a given specimen of urine containing bile pigment.

TABLE 3.—*Protocols of Experiments*

No.	Volume of Urine, C.c.	Phenolsulphonephthalein Added, C.c.[6]	Phenolsulphonephthalein Estimated, per Cent.	Phenolsulphonephthalein Loss, per Cent.	Color Comparison
1	150	0.1	5	50	Poor
	150	0.3	20	33	Fair
	150	0.5	35	30	Fair
	150	0.8	52	35	Fair
2	250	0.2	15	25	Good
	250	0.4	30	25	Good
	250	0.6	50 (?)	17 (?)	Good
	250	1.0	70	30	Good
3	150	0.20	15	20	Poor
	150	0.35	27	23	Fair
	150	0.50	40	20	Fair
	150	0.75	55	26	Fair
	150	1.00	80	20	Good

From Table 3 the following conclusions may be drawn:

(*a*) The quantity of adsorbed phenolsulphonephthalein in a given specimen of urine whose pigments have been precipitated by barium hydroxid is approximately a constant within certain limits of dye concentration.

(*b*) Given a jaundiced urine containing an unknown amount of phenolsulphonephthalein, after the determination of the dye, the quantity lost by adsorption may readily be estimated if to an aliquot portion of the phenolsulphonephthalein containing urine a known amount of dye

6. Occasionally from 0 per cent. to 30 per cent. of dye in other series gave figures which were not as close to the curve as those listed. Careful repetition of these revealed no discrepancy between the theoretical and experimental value except when extraneous pigment interferred or not enough barium hydroxid was used. With a concentration of the dye, say 25 per cent. there is quite a difference in the percentage adsorption if the reading taken is 22 per cent. or 18 per cent. The former gives a value of 12 per cent., the latter 28 per cent. It is obvious that such a close estimation cannot often be made, but yet it does not interfere with the value of the knowledge of the adsorption curve.

is added and the total dye then be determined similarly. The total should not be greater than 100 per cent. The percentage adsorbed then may be found as follows: x equals the percentage of phenolsulphonephthalein determined in specimen containing unknown quantity of dye; k equals the percentage of phenolsulphonephthalein added to aliquot portion; p equals the percentage of phenolsulphonephthalein determined in aliquot portion containing known plus unknown quantities; $p - x$ equals the percentage of phenolsulphonephthalein of added known not adsorbed per unit mass of precipitate; $\frac{p-x}{k}$ equals the fraction of k not adsorbed per unit mass of precipitate; $\frac{x}{\frac{p-x}{k}} = \frac{kx}{p-x}$ equals x′, the final corrected reading for adsorption.

Theoretically, it may be expected that for similar microdeterminations of dyes where adsorption occurs, the correction for adsorption may be obtained in the same fashion.

(*c*) The greater the concentration of dye, the more accurate is the colorimetric comparison.

IV. THE PHENOLSULPHONEPHTHALEIN TEST IN JAUNDICE

The method devised from the studies on adsorption differs from the routine as follows: When there is no correction for adsorption:

1. It is preferable to give the dye intravenously but intramuscular injection is almost as suitable.

2. Divide the two hour specimen into two equal parts.

3. To one part add an excess (urine volume plus 50 c.c.) of saturated barium hydroxid. Dilute to 500 c.c. or 1,000 c.c. Filter. Compare a portion of the filtrate with standards. If the 500 c.c. dilution is used, the reading is direct. If 1,000 c.c. is the dilution, the two hour excretion is the reading $\times 2$. It is of course only necessary to catch a few cubic centimeters of the filtrate. The dilution to 2 liters aids in colorimetric comparison.

4. If the total two hour percentage of excretion of dye is normal or only 5 or 10 per cent. below the lower limits of normal, the reading stands as the excretion of the dye and the excretion may be considered normal.

When correction for adsorption must be evaluated:

5. If the reading obtained is below normal, it must be determined whether the diminished excretion of the dye is actual or is due to adsorption. To the remaining half of the excreted urine, whose dye content has been determined, add 0.25 c.c. (for 500 c.c. dilution) or 0.50 c.c. (for 1,000 c.c. dilution) of phenolsulphonephthalein. With intense jaundice and large urine volume the latter is preferable. Redetermine, in this control, the percentage of dye.

6. The second reading in (5) minus the first in (4) gives the quantity of dye not adsorbed. For example, if the first reading (apparent two hour excretion) had been 20 per cent., and if to the remaining portions 0.25 c.c. of the dye had been added, the second reading, granting that none had been lost by adsorption, would be 20 per cent. plus 50 per cent. (0.25 c.c. dye to 500 c.c.) or 70 per cent. If the reading was 50 per cent. instead of 70 per cent., it is evident that the added dye only gave an additional 50 per cent. minus 20 per cent., or 30 per cent. of color. Hence, three-fifths of the dye added was determined, and two-fifths lost by adsorption.

7. The final reading corrected of excreted dye is equal to the first reading divided by the fraction not adsorbed or following the foregoing example: $\frac{20\%}{3/5} = 20\% \times 5/3 = 33\%$

SUMMARY

1. The indiscriminate use of alcoholic zinc acetate or saturated barium hydroxid to remove bile pigments from urine containing phenolsulphonephthalein in jaundice may give erroneous readings, because of adsorption of the dye.

2. A relatively more accurate method using saturated barium hydroxid as precipitant is described, in which the loss of dye by adsorption may be estimated.

ADHESIONS IN THE UPPER RIGHT ABDOMEN

A CLINICAL TEST COMPARED WITH THE ROENTGEN-RAY FINDINGS *

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In 1922 Lyon [1] described a new clinical test for determining the presence of adhesions in the upper right quadrant of the abdomen. This test is based on the transmission of the musical note of a tuning fork, placed in contact with the skin over the liver, to the bell of a stethoscope placed over the stomach. In his article Lyon stated that this method had been checked against roentgen-ray and operative findings, but he gave no statistics as to the result in a series of cases. It was this fact that prompted the present investigation.

In the present stage of the development of diagnostic procedures the roentgen ray, in competent hands, offers the most reliable method short of visual inspection, for the determination of adhesions in the upper right abdomen. It therefore seemed worth while to compare the new method with the old, keeping in mind, however, the possibility of error in the interpretation of the roentgen-ray study.

This test is described by Lyon as: "an accurate clinical method of determining adhesions between the stomach and neighboring viscera, but particularly useful for the detection of adhesions between the pyloroduodenal segments and the under surface of the liver or other parts of the gall tract."

THE TEST

The test is performed with the patient recumbent and the abdomen and lower thorax exposed. A tuning fork (a G fork of 410 vibrations was used) is struck gently against a solid object, and with the bell of the stethoscope over the stomach in the left hypochondrium, the lower border of the stomach is mapped out by applying the stem of the fork to the abdominal wall in the following manner. The stem should be applied firmly and at right angles to the surface of the abdomen and the note of the fork should not be too loud. Beginning below the level of the umbilicus at first the note heard through the stethoscope will be faint and distant, but as the fork is successively applied closer to the

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1. Lyon, B. B. V.: Surg., Gynec. & Obst. **35**:232 (Aug.) 1922.

costal margin this note will abruptly change to a sharp clear tone when the stem of the fork is placed above the lower border of the stomach. This change has no relation to the proximity of the tuning fork to the stethoscope. Having in this way determined the true gastric note, the fork is then moved toward the right costal margin until this note is lost or the rib margin reached. The transmission is then tested through the liver by placing the stem of the fork above the right costal margin. In placing the stem of the fork on the abdomen, care must be taken that the skin is not put under tension between the fork and the bell of the stethoscope, or a sharp musical note will be transmitted superficially. In placing the bell of the stethoscope below the left costal margin the question of an underlying colon may be raised but this can be ruled out by placing the stethoscope above the costal margin and again determining the lower border of the stomach.

INTERPRETATION OF TEST

As to the interpretation of this test Lyon says:

> In normal cases one does not ever get the tuning fork note transmitted constantly through the liver to the bell of the stethoscope placed over the stomach.
>
> In pathologic cases, however, I have learned to differentiate the following types.
>
> First, when the musical tuning fork note is transmitted from the left half of the right costal margin and this phenomenon is found to be constant at each examination, I would expect to find rather slight formation of adhesions between the pylorus or duodenum and the peritoneal coverings in the neighborhood of the gall ducts.
>
> Second, when the note is transmitted from the costal margin in the region of the ninth and tenth ribs, but is not transmitted through the liver, I would expect to find at operation that the adhesions are more likely to involve the gallbladder.
>
> Third, when the musical note is transmitted from the tuning fork along the length of the right costal margin from the epigastric border to the anterior axillary line, and is very clear and distinct and is always constant, I would expect to find rather older and denser adhesions attached to the looser neighborhood structures, gall ducts, gallbladder and gastrohepatic omentum.
>
> Fourth, when the tuning fork note is constantly transmitted through the liver and heard above the right costal margin, I would expect to find adhesions between the pylorus or duodenum and the under surface of the liver. The clear distinctness of the transmitted note and its wider distribution over a larger area of the liver suggests that the adhesions are denser in character or more widespread. All these tuning fork transmissions of the gastric note will be enhanced if 3 or 4 ounces of air is injected into the stomach.

With all these minutiae of differential diagnosis I cannot agree, especially when unsupported by the definite evidence of a large series of cases, carefully studied at operation or at necropsy. In spite of this I do believe that the transmission of the tuning fork note from the stomach to the right costal margin is not found in normal cases, and is strong clinical evidence of adhesions in the upper right abdominal quadrant. Of course this test, like all other clinical procedures, is influenced

by the personal equation and differences in interpretation, but familiarity with the differences in transmission in normal and pathologic cases will prove a great aid in the study of the upper right abdomen.

COMMENT

As to the rationale of this test, I believe that it is based on certain physical facts. When adhesions unite the pyloroduodenal segment to the under surface of the liver, or to other structures, such as the gall-bladder, which are in anatomic union with the liver, there is formed a continuity of anatomic structure between the liver and the walls of the stomach. If now the stem of the vibrating tuning fork is placed over the liver, the vibrations are transmitted directly from that organ to the walls of the stomach. The air bubble, which in the dorsal position lies in the left hypochondrium, acts as a resonator for the vibrations, amplifying them so that they can be heard by the overlying stethoscope. Mere apposition of structures does not produce the same sharp clear note, because the vibrations are dampened in passing from one structure to the other. An every day example of this is the toy telephone, consisting of two cylinders each closed at one end by a diaphragm and connected by a taut string. The voice is readily transmitted by the string, whereas if the cylinders were placed on each side of a wall no sound would be transmitted.

The patients forming the present series of cases were selected because they all had a complete gastro-intestinal roentgen-ray study. The tuning fork test was done in the course of the routine physical examination at the patient's first visit and the results recorded at that time. The roentgen-ray studies were made at a later date, usually within a week. It might be said here that the roentgenologist did not know that any comparison of his findings with another method was being made. Only the result of the first tuning fork test is recorded here so that there would not be the unconscious influence of a knowlege of the roentgen-ray findings. A total of fifty cases is reported.

In thirty-five of these cases the tuning fork test and the roentgen-ray findings agree (Table 1). In explanation of the large number of positive findings it might be said that these patients were studied in a gastro-intestinal clinic and only those in whom an organic lesion was suspected were roentgenogrammed. In six cases the tuning fork test was positive but the roentgen ray, while showing pathologic changes in the upper abdomen, did not definitely demonstrate adhesions in the right quadrant (Table 2). In these cases the presumption of adhesions is strong, as they all show evidence of inflammatory conditions in the upper abdomen, and therefore they are closely associated with the cases in the first group. In nine cases the tuning fork and the roentgen-ray findings did not agree (Table 3).

TABLE 1.—*Cases in Which the Tuning Fork and Roentgen-Ray Findings Agree*

Case	Tuning Fork	Roentgen-Ray Findings in Upper Abdomen
1	Positive....	Periduodenal adhesions, partial obstruction
2	Positive....	Adhesions causing definite deformity of duodenum
3	Positive....	Second portion of duodenum constricted from ulcer or adhesions
4	Positive....	Duodenum irregular, persistent cicatricial duodenal ulcer
5	Positive....	Duodenum irregular, probable adhesions
6	Positive....	Duodenal adhesions, second portion
7	Positive....	Adhesions to second portion of the duodenum
8	Positive....	Organic obstructive lesion involving pylorus
9	Positive....	Periduodenal adhesions
10	Positive....	Periduodenal adhesions
11	Positive....	Perihepatic adhesions
12	Positive....	Duodenum irregular, possible periduodenal adhesions
13	Positive....	Perigastric and periduodenal adhesions
14	Positive....	Probable periduodenal adhesions or bands
15	Positive....	Diverticulum second portion of duodenum, adhesions in upper right quadrant
16	Positive....	Periduodenal adhesions
17	Positive....	Probable periduodenal adhesions
18	Positive....	Periduodenal adhesions with adhesions to the hepatic flexure
19	Positive....	Periduodenal adhesions
20	Positive....	Periduodenal adhesions
21	Positive....	Periduodenal adhesions
22	Positive....	Periduodenal adhesions
23	Positive....	Periduodenal adhesions
24	Positive....	Persistent deformity of the duodenal cap
25	Positive....	Periduodenal adhesions
26	Positive....	Periduodenal adhesions
27	Positive....	Duodenum shows irregular filling due to ulcer
28	Positive....	Periduodenal adhesions
29	Negative....	Duodenum negative
30	Negative....	Duodenum negative
31	Negative....	Duodenum negative
32	Negative....	Duodenum negative
33	Negative....	Duodenum negative
34	Negative....	Duodenum negative
35	Negative....	Duodenum shows no filling defect or delay

TABLE 2.—*Cases in Which There Is Roentgen-Ray Evidence of Pathology in the Upper Abdomen but No Involvement of Duodenum*

Case	Tuning Fork	Roentgen-Ray Findings
1	Positive....	Probable prepyloric ulcer, duodenum negative
2	Positive....	Duodenum flattened but not fixed
3	Positive....	Probable cholecystitis, duodenum negative
4	Positive....	Adhesions in upper left quadrant involving stomach and splenic flexure
5	Positive....	Duodenitis? Gastric hypermotility
6	Positive....	Small persistent incisura on the lesser curvature just prepyloric

TABLE 3.—*Cases in Which the Tuning Fork and Roentgen-Ray Findings Do Not Agree*

Case	Tuning Fork	Roentgen-Ray Findings
1	Positive....	No evidence of gastro-intestinal pathologic condition
2	Positive....	No evidence of gastro-intestinal pathologic condition
3	Positive....	Chronic appendicitis; duodenum negative
4	Positive....	No gastro-intestinal pathologic condition
5	Negative....	Duodenal adhesions with evident constriction
6	Negative....	Periduodenal adhesions with obstruction
7	Negative....	Periduodenal adhesions
8	Negative....	Adhesions probably between duodenum and gallbladder
9	Negative....	Probable duodenal ulcer. Filling irregular

TABLE 4.—*Percentage of Cases*

Tuning Fork	Roentgen Ray	Cases	Per Cent.
Positive	Positive	28	74
Positive	Probable	6	15
Positive	Negative	4	11
		38	100
Negative	Negative	7	58
Negative	Positive	5	42
		12	100

Grouping these findings a little differently (Table 4) it will be seen that a positive tuning fork test, interpreted as strong presumptive evidence of adhesions, was present in thirty-eight cases. In 74 per cent. of these thirty-eight cases the roentgen-ray study demonstrated the presence of adhesions in the upper right quadrant. In an additional 15 per cent. the roentgen ray showed an inflammatory condition in the upper abdomen. This makes a total of 89 per cent. of those cases giving a positive tuning fork test in which the roentgen ray was able to demonstrate definite upper abdominal pathologic changes. In only 11 per cent. of the cases was the positive tuning fork test not confirmed by the roentgen-ray study. Of the twelve cases with negative tuning fork test the roentgen-ray study was in agreement in 58 per cent.

It is realized that in presenting this study the number of cases is small, and that the wisdom of checking one clinical method against another of less than 100 per cent. accuracy is questionable. Still, as all such tests are influenced by the personal equation, it seemed justifiable to give voice to an impression, and my experience with this test has led me to the belief that it is of material aid in the clinical study of the upper abdomen. It is also hoped that some investigator with the material will compare this test with the findings on visual inspection.

SUMMARY

1. A little used test for adhesions in the upper right abdomen is compared with the roentgen-ray findings.

2. A total of fifty unselected cases is reported.

3. A positive tuning fork test is found to be strong presumptive evidence of an inflammatory condition in the upper abdomen, with adhesions to the under surface of the liver, being in agreement with the roentgen-ray findings in 89 per cent. of the cases.

4. A negative tuning fork test is not of so great value, as it was in agreement with the roentgen-ray findings in only 58 per cent. of the cases.

THE INFLUENCE OF DIFFERENT KINDS OF OIL, INTRODUCED INTO THE RECTUM, ON GASTRIC SECRETION *

W. N. BOLDYREFF, M.D.
AND
J. H. KELLOGG, M.D.
BATTLE CREEK, MICH.

For many years in his clinical work one of us (K.) noticed that different kinds of oil, when introduced into the rectum of a patient in the evening had a harmful effect on digestion the next day; with a lack of appetite, heavy stomach, coated tongue and other symptoms of gastric disorder. He concluded from this that gastric secretion is inhibited by such a use of oils. The experiments of Pawlow [1] and his pupils (Lobasoff,[2] Virshubsky,[3] Sokoloff [4] and others) have proved that oils are inhibitors of gastric secretion, and that the inhibition has its origin in the mucosa of the small intestine.

Kellogg [5] explained the mechanism of this inhibiting effect, in the patients observed by him, by the following fact, which had been noted and proved in this clinic by Case.[6] It was found that with the roentgen ray one could frequently observe rapid and numerous reverse movements of the contents of the rectum through the ileocecal valve up into the small intestine. Evidently this state is not infrequent in patients where this valve does not quite fulfil its function of preventing the contents of the rectum from going back. This observation is in full agreement with the suggestions of German authors (Grützner,[7] Swiezynsky,[8] Reach,[9] Uffenheimer,[10] and Kast [11]) regarding the hitherto unexplained

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* From the Pawlow Physiological Institute of the Battle Creek Sanitarium.

1. Pawlow, I. P.: The Work of the Digestive Glands, London, Griffin & Co., Ltd., 1910.
2. Lobasoff, I. O.: Dissertation, Petersburg, 1896.
3. Virshubsky, A. M.: Dissertation, Petersburg, 1900.
4. Sokoloff, A. P.: Dissertation, Petersburg, 1904.
5. Kellogg, J. H.: Incompetency of Ileocecal Valve, M. Rec. June 21, 1913.
6. Case, J. T.: X-Ray Studies of the Ileocecal Region and the Appendix, Am. J. Roentgenol. **4**:77-111, 1912.
7. Grützner, P.: Zur Physiologie de Darmbewegung, Deutsch. med. Wchnschr. **48**:897, 1894.
8. Swiezynsky, I.: Nachprüfung d. Grutzner'schen Versuche über das Schicksal von Rectalinjectionen an Menschen und Tieren.
9. Reach, F.: Ueber rücklaüfige Fortbewegung von Darminhalt, Prag. med. Wchnschr. **44**:549, 1902.
10. Uffenheimer, A.: Weitere Studien über d. Durchlässigkeit d. Magendarmkanales für Bacterien, Deutsch. med. Wchnschr. **46**:1851, 1904.
11. Kast, L.: Rücklaüfige Stromung in der Speiseröhre als Erklärung der belebten Zunge, Berl. klin. Wchnschr. **28**:947, 1906.

regurgitation of small particles (lycopodium, grains of starch, grains of different insoluble dyes, etc.) and of microbes (*B. prodigiosus*) from the rectum up into the small intestine, and even up to the stomach and the mouth.

Although these conclusions, and especially the methods by which they were reached, were severely, and not without reason, criticized by various authors (Christomanos,[12] Platenga [13]), still they deserve serious attention, the more so because the phenomena of the reverse movement of the contents of the intestines, both at the lower end of the small intestine and at its beginning, are firmly established.

Because of the clinical importance and the physiologic interest of the before-mentioned observations, Kellogg suggested that this question should be investigated experimentally. The investigation was carried on in the sanitarium.

First of all it was necessary to find out which oils and in what degree have an inhibiting effect on digestion in the stomach when introduced into the rectum. Then it was necessary to seek for the source of this inhibition; i. e., does the inhibiting reflex start from the rectum, from the end of the small intestine, or from both places?

The experiments of Boldyreff,[14] Pflüger,[15] Popelsky,[16] Studsinsky [17] and others have proved that in oils the active principle with respect to the secretory and the motor activity of the digestive tract are fatty acids. Therefore the oils most rich in these acids and most capable of being split with the formation of these acids are, when introduced into the rectum, the strongest inhibitors of digestion in the stomach. To be sure, this fact has only a theoretic significance because, first, the commercial oils used in clinics and laboratories always contain free fatty acids; and, second, even if the oils used are neutral when introduced in the stomach or the duodenum they soon begin to split, forming fatty acids because of the action of the traces of ferments always found on the mucosa of the digestive tract.

In order to obtain conclusive results, it was decided to conduct experiments on a number of dogs, and to investigate the inhibiting effect of oils both on the psychical side of digestion (appetite and the first phase of digestion) and on the chemical (second phase of digestion).

12. Christomanos: quoted by Swiczynsky.
13. Platenga: quoted by Reach.
14. Boldyreff, W. N.: Der Uebertritt des natürlichen Gemisches aus Pancreassaft, Darmsaft und Galle in den Magen, Arch. f. d. ges. Physiol. **121**:13, 1907.
15. Pflüger, E.: Arch. f. d. ges. Physiol. **90**:1, 1902.
16. Popelsky, L.: Dissertation, St. Petersburg, 1896.
17. Studsinsky: Rusk. Vrach., 1911, Nos. 1, 2 and 3.

The experiments were conducted on dogs with gastric fistulas and with esophagotomy.

In the first series of experiments, the secretion of gastric juice was caused by merely showing tasty food (meat, bologna, etc.), to the dog; in the second series by means of "sham" feeding. After the normal quantity of secretion was determined and the qualities of the juice, acidity (hydrochloric acid) and pepsin contents (after Mett), were tested, the experiments with oils were begun.

Different oils were used in quantities ranging from 50 to 100 gm.; the oils were introduced into the rectum at various time intervals (five,

TABLE 1.—*Influence of Oils on Gastric Secretion: Excitation by Showing Meat*

1. Norm		2. Oil Experiment	
Experiment No. 31. 1923. Dog No. 4. Fed 18 hours previously; stomach empty; reaction alkaline		Experiment No. 30. 1923. Dog No. 4. Fed 18 hours previously 300 gm. boiled meat and about 600 c.c. oatmeal gruel; 10 hours previously 100 c.c. cod liver oil introduced in rectum; stomach almost empty (less than 5 c.c. food); reaction acid	
Minutes	Juice, C.c.	Minutes	Juice, C.c.
		0 - 5	3.5
		5 - 10	0.9
0 - 5	0.0	10 - 15	0.6
5 - 10	0.0	15 - 20	0.6
		20 - 25	0.4
		25 - 30	0.5
Excitation Started		Reaction Alkaline; Excitation Started	
0 - 5	2.0	0 - 5	0.0
5 - 10	6.0	5 - 10	2.0
10 - 15	9.0	10 - 15	4.0
15 - 20	7.5	15 - 20	2.5
	24.5		8.5
Excitation Stopped		Excitation Stopped	
20 - 25	5.0	20 - 25	3.0
25 - 30	2.5	25 - 30	2.0
30 - 35	2.5	30 - 35	1.5
35 - 40	0.0	35 - 40	0.5
Acidity of juice collected during excitation .....0.30 per cent.		Acidity of juice collected during excitation .....0.28 per cent.	
Mett's test of the same juice...0.09 inches		Mett's test of the same juice...0.08 inches	

six and ten hours) before the experiments. The following oils were tested: mineral oils (liquid paraffin), vegetable oils (olive and linseed), and animal oils (butter and cod liver oil).

In general, the oils introduced into the rectum had a strong inhibiting effect on the quantity of gastric juice secreted, decreasing the secretion to one-half or one-third, normal, but they did not change the acidity or the pepsin content of the juice. Thus we see a difference between the inhibiting action of oil introduced into the rectum and that introduced into the stomach. In the latter case it decreases also the acidity and the pepsin content of the juice.

TABLE 2.—*Influence of Oils on Gastric Secretion: Excitation by Sham Feeding*

1. Norm

Experiment No. 4. July 16, 1923. Dog No. 8. Weight of dog, 16,500 gm. Fed 13 hours previously (500 gm. meat); stomach empty; reaction acid

Minutes	Juice, C.c.
0 – 5	2.8
5 – 10	3.2
10 – 15	2.6
15 – 20	2.5
20 – 25	2.6
25 – 30	2.1
Sham Feeding Started	
0 – 5	5.4
5 – 10	21.7
10 – 15	27.5
15 – 20	23.1
20 – 25	20.3
25 – 30	18.0
	116.0

Sham Feeding Stopped

Acidity of juice collected during sham feeding.....0.54 per cent.
Mett's test of same juice.....0.09 inches

2. Oil Experiment

Experiment No. 22. Aug. 10, 1923. Dog No. 8. Weight of dog 18,100 gm. Fed 13 hours previously 500 gm. meat and 100 gm. bread; stomach empty; reaction acid. 11 hours previously 100 c.c. olive oil introduced into rectum and remained there

Minutes	Juice, C.c.
0 – 5	0.0
5 – 10	0.0
10 – 15	0.0
15 – 30	0.0
Sham Feeding Started	
0 – 5	2.6
5 – 10	11.0
10 – 15	8.2
15 – 20	2.1
20 – 25	4.4
25 – 30	5.1
	33.4

Sham Feeding Stopped

Acidity of juice collected during sham feeding.....0.46 per cent.
Mett's test of same juice.....0.10 inches

TABLE 3.—*Influence of Different Oils, Introduced into the Rectum, on The Gastric Secretion: Excitation by Showing Meat* *

Date of Experiment, 1923	Juice, C.c.	Acidity, per Cent.	Pepsin (after Mett)	Norm or Kind of Oil	Dog Number
April 30	40.0	0.30	0.08	Norm	25
June 10	25.6	0.24	0.11	Norm	25
June 29	16.0	0.31	0.08	Norm	4
July 2	22.0	0.23	0.10	Norm	9
July 18	24.5	0.30	0.09	Norm	4
September 6	18.5	0.30	0.09	Norm	6
May 6	1.4	....	....	Olive oil	25
August 6	3.9	0.22	0.11	Olive oil	9
August 13	10.1	0.24	0.11	Olive oil	9
May 3	17.8	0.29	0.07	Linseed oil	25
May 14	16.0	0.23	0.06	Linseed oil	25
July 12	8.5	0.28	0.08	Cod liver oil	4
May 8	47.5	0.52	0.10	Butter	25
May 6	43.6	0.40	0.00	Paraffin oil	25
May 16	25.5	0.28	0.00	Paraffin oil	25

* Juice in each case was collected for twenty minutes.

TABLE 4.—*Influence of Oils on Gastric Secretion: Sham Feeding* *

Date of Experiment, 1923	Juice, C.c.	Acidity, per Cent.	Pepsin, (after Mett)	Norm or Kind of Oil
July 16	116.0	0.54	0.09	Norm
August 8	92.4	0.48	0.09	Paraffin oil
August 10	33.4	0.46	0.10	Olive oil
August 13	47.7	0.44	0.12	Cod liver oil
August 17	68.7	0.43	0.10	Linseed oil
August 20	108.6	0.50	0.14	Norm

* Juice in each case was collected for thirty minutes.

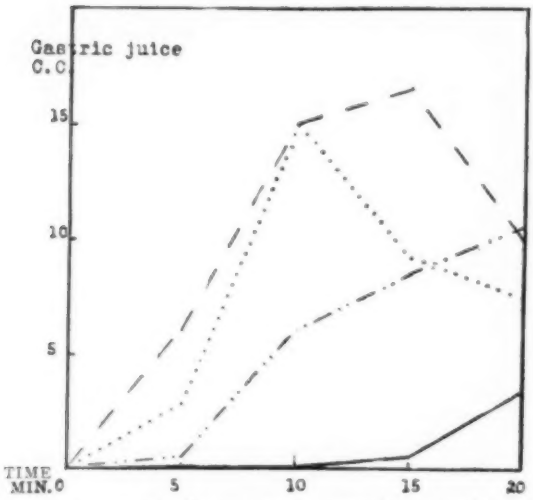

Chart 1.—Influence of oils on gastric secretion. Straight line, olive oil; broken line, butter; dot and dash, paraffin oil; dots, norm (average of three experiments).

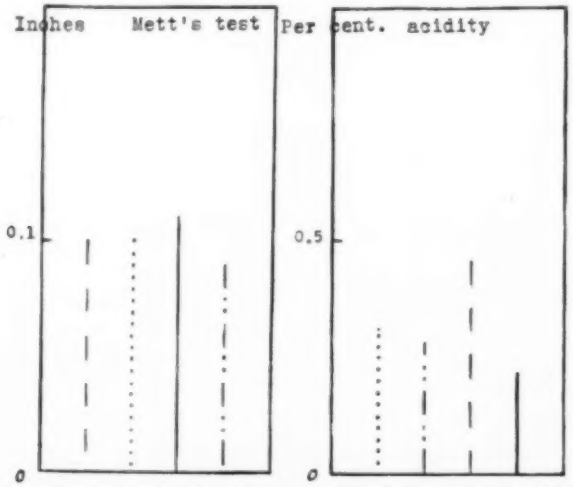

Chart 2.—Excitation by showing meat. The juice was collected for twenty minutes in each case.

This inhibition is observed in cases of "appetite secretion" as well as in the case of "sham" feeding secretion of gastric juice.

Altogether forty experiments were conducted on dogs, the results of which are given in the tables and charts.

The mineral oil did not have any inhibiting effect, nor did the butter cause any inhibition, presumably because it is not liquid at body temperature, but is a viscous, thick mass which cannot move from the

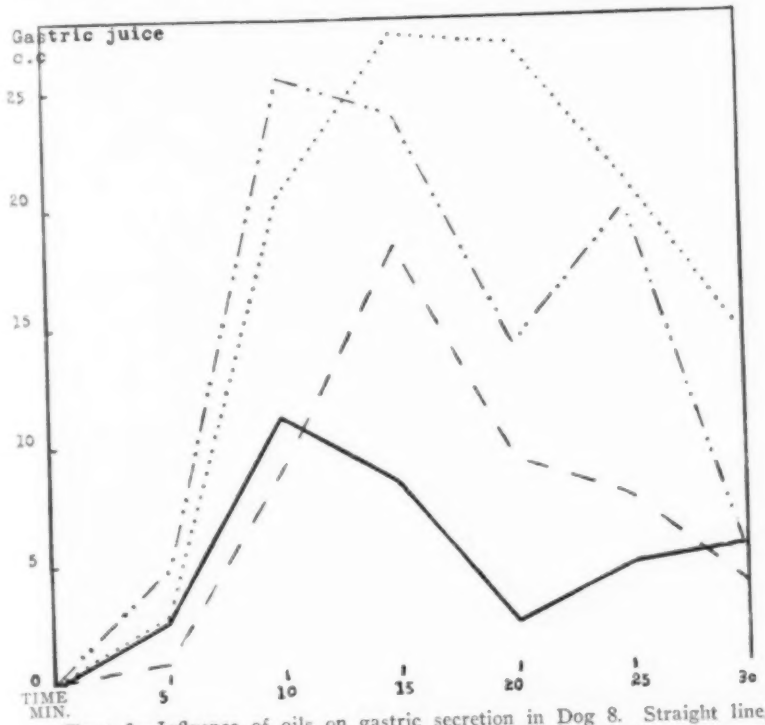

Chart 3.—Influence of oils on gastric secretion in Dog 8. Straight line, olive oil; broken line, cod liver oil; dot and dash, paraffin oil; dots, norm (average of two experiments).

rectum into the small intestine and therefore cannot develop its inhibitory action.

After the introduction of the oil, each dog was placed alone in a room with a smooth floor, and careful observation was made as to whether the oil remained in the rectum until the time of experimentation. If even a small part of oil escaped, the experiment was not conducted at all. In this way it was found that the active dose of oil is a quantity ranging from 50 to 100 c.c.

The works of Heidenhain,[18] Pawlow,[1] Boldyreff [19] and others have proved that the acidity of the gastric juice as secreted from the glands of the stomach is always constant; the variations in its acidity, especially when the quantity of gastric juice is small (Tables 1 and 3), depend on different alkaline admixtures, added either from the stomach itself (gastric mucus) or from the duodenum (pancreatic juice and other intestinal juices).

Cod liver oil was found to produce a less strong inhibition, evidently because during its use it was almost impossible to get rid of its strong fishy odor; and the products made from fish, as has been shown by experiments of Boldyreff,[20] cause an abundant secretion of gastric juice.

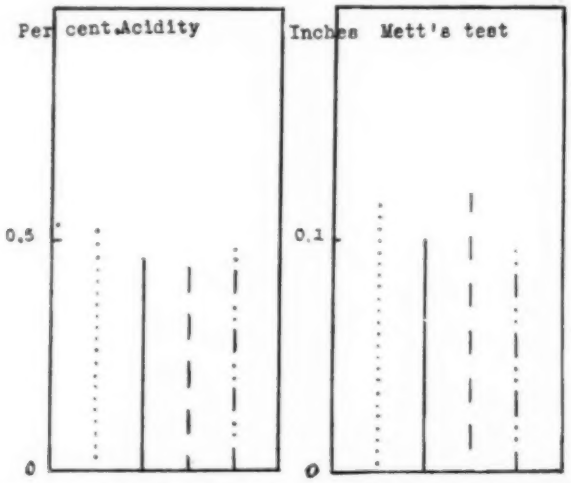

Chart 4.—Sham feeding. The juice was collected for thirty minutes in each case.

EXPERIMENTS WITH NEUTRALIZED OIL

Occasionally experiments were carried out on a dog with a catarrhal affection of the stomach, in conditions somewhat pathologic and therefore corresponding to those of hospital or clinic observation. Results were the same.

The inhibition of gastric secretion by neutral oils begins after a longer period of time after the introduction of oil into the rectum than in case of commercial oils, containing free fatty acids.

The results obtained show that great care should be taken in the oil treatment of patients with certain kinds of stomach disorder.

18. Heidenhain, R.: quoted by Pawlow.
19. Boldyreff, W. N.: Quart. J. Exper. Physiol. **7**:1-12, 1915.
20. Boldyreff, W. N.: Boas' Arch. **15**:1, 268, 1909.

TABLE 5.—*Inhibiting Action of Neutral Olive Oil as Gastric Secretion: Sham Feeding* *

Date of Experiment 1923	Kind	Juice, C.c.	Acidity, per Cent.	Pepsin (after Mett)	Remarks
	Mean normal	111.7	0.49	0.10	Control
August 10.....	100 c.c. olive oil (not neutralized) introduced in rectum 11 hours before experiment	33.4	0.45	0.10	Inhibition
September 28...	100 c.c. neutral olive oil introduced in rectum 12 hours before experiment	121.3	0.49	....	No inhibition
October 1.....	.....	61.3	0.48	....	Inhibition
November 16...	100 c.c. neutral olive oil introduced in rectum 12 hours before experiment	106.1	0.5	0.10	Slight inhibition
November 21...	100 c.c. neutral olive oil introduced in rectum 11 hours before experiment	109.7	0.4	0.09	Almost no inhibition
November 22...	.....	49.6	0.5	0.10	Inhibition

* Juice in each case was collected for thirty minutes.

TABLE 6.—*Influence of Olive Oil Clysters on Weight of a Sick Dog*

Date	Weight, Gm.	
September 28	17,800	Neutral oil introduced
September 29	17,600	
October 2	17,400	
October 4	17,000	
October 5	17,200	
October 7	17,400	
October 19	17,800	
October 23	17,800	
October 30	17,900	
November 7	18,100	
November 16	18,100	Neutral oil introduced
November 17	17,900	
November 18	17,600	
November 19	17,500	
November 21	17,500	Neutral oil introduced
November 22	17,500	
November 23	17,200	
November 24	17,400	
November 30	17,500	
December 9	17,600	

SUMMARY

The action of oils introduced into the rectum.

1. The mineral oils (liquid paraffin oil) do not diminish the appetite, and do not have any harmful effect on gastric digestion.

2. Of the animal oils, butter has no inhibiting action on digestion because it is not liquid at body temperature, and therefore cannot move into the small intestine. Cod liver oil inhibits digestion, but in a relatively small degree.

3. The vegetable oils (olive oil and linseed oil) inhibit very strongly the psychical phase of digestion.

4. The fatty acids are the active substance in the oils.

5. Commercial oils have a stronger inhibitory action, as they contain free fatty acids, but neutral oil also possesses this action, though in a less degree. Moreover, the action of neutral oil is slower.

6. The inhibiting action of oils introduced into the rectum consists only in decreasing the quantity of gastric juice; its acidity and pepsin content remain nearly constant.

CORRECTIONS

In the September issue of the ARCHIVES OF INTERNAL MEDICINE, an error occurred in listing "Henry P. Walcott, M.D." as one of the authors of the article, "The Effect of Iodin in Exophthalmic Goiter." The authors of this article are:

PAUL STARR, M.D.
Henry P. Walcott Fellow, Harvard Medical School

HAROLD N. SEGALL, M.D.

AND

JAMES H. MEANS, M.D.

BOSTON

In the article by Drs. Brown and Coffey, published in the October issue, the centerhead, "Cases in which our method was used by others," which precedes the report of Case 9, page 437, should precede the report of Case 10, page 440.

Book Reviews

Charles White and The Arrest of Puerperal Fever. J. George Adami, C.B.E., M.D., F.R.S., Vice-Chancellor of the University of Liverpool. London, Hodder and Stoughton, Ltd., Price, $5.00.

This work contains the inaugural Lloyd Roberts Lecture delivered by the author before the Manchester Royal Infirmary, and an exhaustive collation of the writings of Charles White on puerperal fever.

The lecture is a plea for just recognition of the work of Charles White and his English contemporaries in the prevention of puerperal fever, years before Semmelweis published his "Aetologie."

Indeed, Dr. Adami demonstrates that White's "Treatise on the Management of Pregnant and Lying-In Women," published in 1773, demanded practically all the prophylactic measures insisted on by Semmelweis eighty years later; and that in 1826-1833 Collins, master of the Rotunda, was able to reduce the hitherto appalling mortality from puerperal fever at that institution to a minimum by the use of chlorinated lime and general adherence to the recommendations of White.

Five editions of White's treatise were published during the twenty years succeeding its initial publication, translations appearing in both German and French.

Of more than passing interest today is White's insistence on the importance of his patients sitting up as early as the second or third day, and its relation to womb drainage and foul and retained lochia.

Paleopathology; an Introduction to the Study of Ancient Evidences of Disease. By Roy L. Moodie, Ph.D., Associate Professor of Anatomy in the University of Illinois. University of Illinois Press, Urbana, Illinois, 1923.

The word Introduction is unduly modest. Dr. Moodie, whose competency has been well demonstrated for a number of years by published articles and demonstrations of original material, has really made an encyclopedic study of an important topic never heretofore handled in the same way. He has followed the geologic record down to about 600 B.C. in the old world and to the late pre-Columbian period in America, and, as he says (Preface): "These studies may be regarded as a synthesis of medical history, paleontology and anthropology." His hope "that the details of ancient pathologic lesions may aid in an understanding of the nature of disease" is reasonable, though its fulfillment depends on the broadness of view of students. The absorbing question of the acquisition of some human diseases from animals in the early ages and the extinction of great groups of animals are some of the problems of paleopathology. As this word was first defined less than thirty years ago it is not strange that so little is known. None of the diseases so far discovered is likely to have directly endangered the life of the individual or the race. As Dr. Moodie says: "Most of the ancient diseases may be regarded as chronic, infectious or constitutional." But evidences of some disease are present in all geologic periods. While an immense fund of knowledge has been assembled by the author he justly says that he has not attempted many generalizations. In rare cases the statements may seem hardly warranted as, in speaking (page 30) of the apparent immunity of early paleozoic animals to infectious diseases. Considering

relatively small proportion of persons and species studied, it seems venturesome to assume that these organisms were free from disease. Equally venturesome seems the statement (page 38) that disease is relatively recent in its origin, and has afflicted the inhabitants of the earth for only the last quarter of its history, or twenty-five million out of a hundred million years. Is it not more likely that from the beginning disease was a close follower on life? But views that excite serious protest are rarely obtruded, and in general the author has observed a wise though critical and objective method of presentation. A brief synopsis of the contents will furnish some idea of the scope and value of the work. The Introduction gives a general sketch of the data, with a table showing the geologic periods and pathologic evidences. Chapter 1 describes the development of paleopathology with an account of the measurement of geologic time. In Chapter 2, on the Origin of Disease, a more detailed table of all geologic evidences of disease is presented. Chapter 3, on Pathological Conditions Among Fossil Plants, is contributed by Dr. Edward W. Berry of Johns Hopkins University, who gives a good account of that important subject. In Chapters 4 and 5, Callus and Fracture in Fossil Vertebrates are very fully illustrated and well described, as are also Deforming Arthritides in the Early Vertebrates. Chapter 6, on Caries and Alveolar Osteitis Among Fossil Vertebrates, may surprise those who look on dental caries as an affliction of high civilization and found only in *homo sapiens*. It may be added that in the Pleistocene fossilized human skeleton recently found in California, and supposed to be twenty-five thousand years old, absorption of the alveolar process and also osteophytes on the vertebrae are evident. Chronic Infections Among Fossil Vertebrates, Parasitism Among Fossil Animals, the Bacteriology of Past Geological Ages, Opisthotonos and Allied Phenomena furnish several more chapters. A short but very interesting chapter considers the Extinction of Races. This is followed by the Pathology of the Early Human Races, beginning with a description of the exostoses on the femur of Pithecanthropos, and including some remarks on Evidences of Syphilis Among Ancient Men and on Prehistoric Trephining, the Use of the Cautery, and amputations of fingers among primitive races. A more detailed discussion of syphilis would be welcome. The author may be correct in his belief that the tubercle of Carabelli (page 354) does not prove the existence of syphilis, but he seems to be at variance with many syphilographers when he states briefly that Hutchinson's teeth " have been recently shown to be due to faulty nutrition." Genuine and pseudo-Hutchinsonism seem to be confused. Chapter 13 on diseases of the Ancient Egyptians very properly begins with a biographical sketch of Sir Marc Armand Ruffer. The details are too numerous even to enumerate and of absorbing interest. Chapter 14 describes Diseases Among the Pre-Columbian Indians of North America and contains a discussion of the antiquity of American Indians. The final chapter describes Diseases of the Ancient Peruvians with accounts of some interestting types, such as gundu, verruga, still widespread, uta or leishmaniaisis, and negua, due to the sand flea or jigger. Prehistoric trephining is here well described and richly illustrated, as are also diseases of the teeth. A very full bibliography and an excellent index add much to the usefulness of the book to students. An excellent feature and one that might well be imitated in many other scientific books is furnished by the biographic notices of authors cited. In many cases there are portraits. The illustrations on 117 plates are very numerous and in general are well produced and illustrate many things of interest besides pathologic changes, such as arrow heads in the tissues, trephining and other prehistoric scenes. The text as a rule is clear and lively but some expressions seem questionable, such as the frequent use of "pathology," "this pathology," for disease, lesions, or alteration. "Sir Ruffer" may be proper usage in revised court circles but in pre-war days would have been incorrect. The University of Illinois Press is to be congratulated on the high quality of

the mechanical execution of the book. No doubt the compositor and proof reader are responsible for the periods after the initials of W. J. McGee. The well known foible of one of the most interesting and most lovable of American anthropologists need hardly be disturbed. The work is a valuable addition to the literatures of both geology and pathology and as such must appeal to a very wide circle.

CLINICAL ASPECTS OF THE ELECTROCARDIOGRAM; A MANUAL FOR PHYSICIANS AND STUDENTS. By HAROLD E. B. PARDEE, M.D. Price $4.00, pp. 236; 56 illustrations. New York, Paul. B. Hoeber, 1924.

This book contains ten chapters, eight of which are devoted to the consideration of the normal and various types of pathologic electrocardiograms. In the former, variations in the curves from normal persons are pointed out, and in the latter the clinical significance of the pathologic variations is discussed. The ninth chapter deals with the theory of electrocardiograms, and the final chapter is devoted to the description and the operation of the Hindle electrocardiograph.

The author has endeavored to give a general summary of the current knowledge of electrocardiology, referring only to those experimental observations which have a direct bearing on the clinical interpretations of the pathologic electrocardiograms. A portion of the chapter on the theory of electrocardiograms is very technical, and it is questionable whether so much space should be devoted to this particular phase of the field in a book of this type.

The chapter on the description of the operation of the Hindle electrocardiograph is especially valuable to the beginner in this field. Instructions as to the operation of the instrument are given in a straightforward manner. The various difficulties that may be encountered are considered and the means of correcting them suggested. In general, the book covers a field, from the standpoint of which it was written, in a credible manner and is recommended to the profession.

HUMAN PROTOZOOLOGY. By ROBERT W. HEGNER, PH.D., Professor of Protozoology, and WILLIAM H. TALIAFERRO, PH.D., Associate Professor of Protozoology in the School of Hygiene and Public Health of the Johns Hopkins University. New York, The Macmillan Company, 1924.

"This book represents essentially the subject matter of the course in protozoology given by the writers in the School of Hygiene and Public Health of the Johns Hopkins University." The hope that it may be useful to students in other institutions and to health officers and physicians, expressed by the writers, seems certain to be realized, for they have made a noteworthy contribution to the subject and one for which there has been a decided need. From the enormous literature on the protozoa they have made a rigid selection, but have omitted nothing that a rather critical search has suggested. While human parasites give the leading motive, many allied forms in lower animals are mentioned and described so fully that the reader cannot fail to keep in mind the broader aspects of protozoology. The plan is to describe "the general biology of the protozoa, as indicated by each group studied, to give typical life histories of representative species, either from man or lower animals, and then to present a more detailed account of the species living in man." While the plan makes it an ideal text book for beginners, the more advanced worker will find it a very convenient reference work, and it should appeal especially to laboratory technicians who are obliged to deal so frequently with problems of pro-

tozoology. A carefully selected bibliography of fifty-two pages and adequate indexes facilitate reference. Wide knowledge of the literature is obvious on all topics. The authors have wisely omitted the minute details of classification that so often needlessly consume the time of the clinical investigator. The chapter on Diagnosis of Intestinal Protozoa is a model of straightforward information. The illustrations, print and paper are unusually good. Mistakes that enter so easily into the first edition of a work containing so many details are rare and comparatively unimportant. A wide use is to be predicted for this work.